June 2005

Science & Technology Review

National Nuclear Security Administration's
Lawrence Livermore National Laboratory

Genomic Mining for Regulatory Elements

Also in this issue:

- Laser Research Builds on Einstein
- Surveillance Gets a Boost with Speckle Imaging
- Detecting Mercury's Gamma Rays in Orbit

About the Cover

Livermore researchers have developed a suite of computational tools to locate regulatory elements in the published genome sequences of many different species, including frogs, fish, mice, and humans. As the article beginning on p. 4 describes, the tools provide a fast and reliable method to efficiently analyze the massive amount of data emanating from public sequencing efforts. Researchers worldwide can access these analytical and visualization tools online. Biologists can test computed predictions using a variety of experimental approaches. The experimental results, in turn, help the Livermore team refine the programs to enhance their performance.

Cover design: Kitty Madison

About the Review

Lawrence Livermore National Laboratory is operated by the University of California for the Department of Energy's National Nuclear Security Administration. At Livermore, we focus science and technology on ensuring our nation's security. We also apply that expertise to solve other important national problems in energy, bioscience, and the environment. *Science & Technology Review* is published 10 times a year to communicate, to a broad audience, the Laboratory's scientific and technological accomplishments in fulfilling its primary missions. The publication's goal is to help readers understand these accomplishments and appreciate their value to the individual citizen, the nation, and the world.

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Science & Technology REVIEW

June 2005

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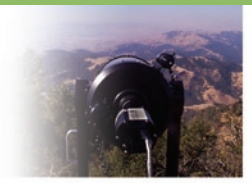

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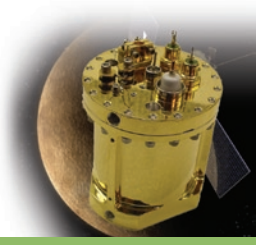

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BlueGene/L breaks its own record

On March 23, 2005, Administrator Linton F. Brooks of the National Nuclear Security Administration (NNSA) announced that the BlueGene/L supercomputer developed through the Advanced Simulation and Computing Program for NNSA's Stockpile Stewardship efforts has performed 135.3 teraops (trillion operations per second) on the industry standard LINPACK benchmark. Installed in the Laboratory's new Terascale Simulation Facility, the machine broke its previous record as the fastest supercomputer in the world. This performance was achieved with only half the BlueGene/L machine. The remaining half will be installed this summer. Last November, just one-quarter of BlueGene/L topped the Top500 List of the world's supercomputers.

"BlueGene/L will address vital challenges critical to ensuring the safety and reliability of the nation's aging nuclear weapon stockpile," says Brooks. "This supercomputer provides an essential resource to the weapons complex, allowing us to address time-urgent and mission-critical scientific issues that require such specialized computational capabilities."

Results of scientific importance have already been attained with only one-quarter of BlueGene/L. Livermore scientists for the first time have performed 16-million-atom molecular dynamics simulations to resolve the key physical effects for successfully modeling pressure-induced, rapid resolidification in tantalum.

"BlueGene/L allows us to address computationally taxing stockpile science issues at very low cost," says Livermore Director Michael Anastasio. "Effective and relatively inexpensive supercomputers of this nature will open doors for scientists across the country."

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Mystery of ice planets unraveled

The conditions in the core of icy, large planets such as Neptune and Uranus are extreme, with pressures of hundred of thousands or millions of times greater than that on Earth and temperatures of thousands of degrees. Under similar conditions, Laboratory scientists have discovered a "superionic" phase of water—neither ice nor liquid—in which the oxygen atoms remain virtually stationary while the hydrogen atoms are extraordinarily mobile.

"This shows how extreme pressures and temperatures can completely transform water from a molecular system into a 'salt' composed of mobile protons and stationary oxygen ions," says Alex Goncharov, a Livermore chemist and lead author of a paper that was published on April 1, 2005, in *Physical Review Letters*. "This phase of water is of profound importance not only to planetary science but also to geoscience and fundamental chemistry."

To re-create the extreme pressure required to force water into the superionic state, Goncharov's team used a diamond anvil cell, which squeezes the water between two diamonds, creating a pressure 470,000 times greater than Earth's atmospheric pressure. The researchers used a laser to heat the water to the intense temperature of 1,500 kelvins. At this pressure and temperature, the water went superionic.

In addition to laboratory experiments, the team used computer models to predict the atoms' behavior, which showed that observed changes in the optical spectra were consistent with a superionic phase. The simulations were performed using Thunder, one of Livermore's terascale computers.

The observations and models have larger implications for the makeup of the universe. There could be more yet unobserved superionic water in the universe than water in solid or liquid forms.

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Study offers new clues to gene deserts

Scientists studying human chromosomes 2 and 4 have uncovered new clues to gene deserts—long stretches of DNA in the human and other mammalian genomes that contain no protein-coding genes. In a paper published April 7, 2005, in *Nature*, Livermore bioinformatics scientist Ivan Ovcharenko and his colleagues revealed that a particular feature of two large gene deserts has persisted through hundreds of millions of years of evolution, even though the DNA sequence within the deserts has changed considerably over time. The deserts are located on either side of two closely related genes active in the human brain and heart.

The fact that the "architecture" of the deserts has persisted over long evolutionary periods could be significant. "We were surprised to see how old the deserts were," says Ovcharenko. "They appeared at a time point that follows the divergence of fish from *Ciona intestinalis* (a sea squirt) but precedes the divergence of mammals from fish. They have no obvious function, but for some reason, they were preserved at that location in the genome. This makes us wonder what's special about these particular gene deserts." Ovcharenko says the information obtained from the analysis of chromosomes 2 and 4 will lead to further study "to see why some genes in the human genome tend to have gene deserts in their neighborhoods."

The *Nature* paper's lead author was LaDeana Hillier at the Genome Sequencing Center (GSC) at Washington University School of Medicine in St. Louis. GSC led the international team that sequenced and analyzed the two chromosomes.

See the article beginning on p. 4 for more work by Ovcharenko on gene deserts.

Contact: Ivan Ovcharenko (925) 422-5035 (ovcharenko1@llnl.gov).

Continued on p. 26

Close Collaborations Advance Progress in Genomic Research

A historical strength of much of the Laboratory's science has been the ability to couple the development of predictive theoretical tools directly to experimental efforts that test the predictions. However, opportunities to exploit this highly productive approach have been rare in biology. The science is changing, and with it, the frequency with which this especially fruitful type of cross-discipline interaction occurs. One example of this interaction is illustrated in the article beginning on p. 4, which discusses the work of bioinformaticist Ivan Ovcharenko working in collaboration with bioscientists Lisa Stubbs and Gabriela Loots.

The team's work addresses the important but difficult challenge of identifying regulatory elements in genomes, which are small patches of DNA responsible for turning genes on or off as changing conditions require. To address this challenge, a suite of software tools is being developed to predict the location of these elements while several experimental approaches are used to test those predictions.

The tools developed by the Livermore team use a number of approaches to identify regulatory elements, but the central theme is an aspect of what biologists call comparative genomics. Here, the key concept is evolutionary conservation. Segments in genomes that encode important functions, such as the regulation of genes, are much more likely to be conserved over evolutionary time than is the rest of a species' DNA. Thus, by comparing the genomes of different creatures, the conserved segments, including regulatory elements, can often be recognized.

By being "embedded" in our biological labs, Ovcharenko has the perfect environment to develop tools of maximum use to biologists. This close relationship ensures, among other things, a process through which tools can be continually honed and validated and at the same time made "biologist friendly." One notable feature of Ovcharenko's tools is the ease with which they can be learned and used by biologists who are unsophisticated in computer science. Indeed, much of what biological researchers need is not high-level computer programs running on supercomputers but personal computer programs written by people who understand biology and biologists.

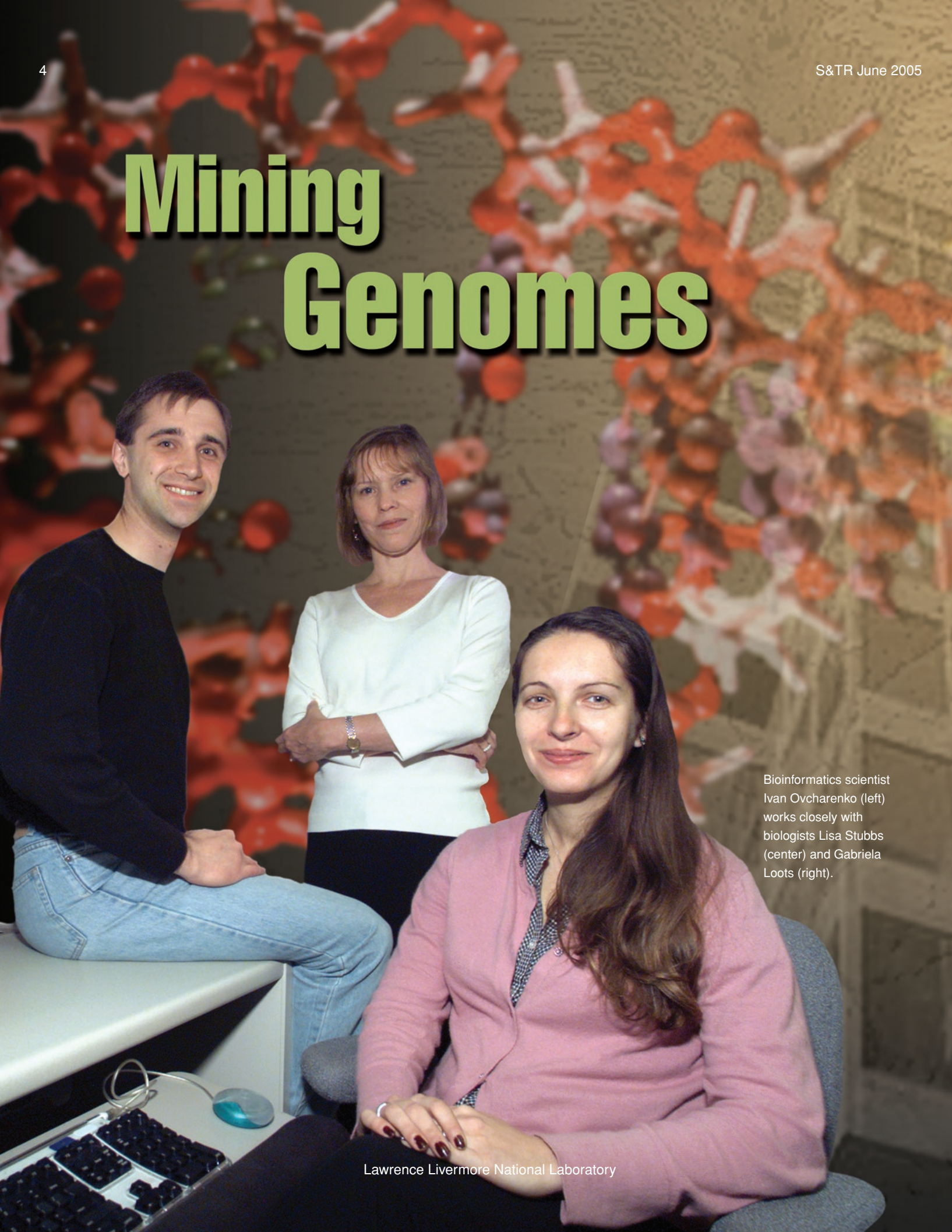
Tools of the kind described in the article are at the forefront of genomic research; they are essential to extracting information from increasingly more extensive Web-accessible genomic data sets covering "all creatures great and small," from bacteria to plants to humans. But they also reflect a profound shift occurring in biological research. That shift, oddly, is one of culture and belief, and of social standards—standards that dictate what approaches to research are acceptable. For a long time, the doctrine of hypothesis testing has dictated how biological science should be done. The idea is that experimental work should be undertaken to test a tightly defined hypothesis—one resting firmly on what is already well established. In stark contrast is a "fishing expedition" (now called discovery-based science) designed to gather information for its own sake in anticipation of what it will teach us. The Human Genome Project was a fishing expedition, and it led to an outpouring of wonderful discoveries that no one could have anticipated or framed as "hypotheses."

Increasingly, biologists are becoming aggressive, free-ranging "hunter–gatherers" of the truth. They are using new high-throughput techniques to produce huge data sets and using computers and the Internet to search them en mass. It is in the contribution they make to this research revolution that the Livermore team's tools have their true significance. They let us ask of our exploding collection of genomes, "What do you have to tell us?" The genomes' answers are stunning, in part because they show us the limitation of adhering exclusively to hypothesis testing.

We are making exciting headway in unraveling the secrets of genomes and therefore of life itself. Obtaining a detailed picture of how genes and other DNA sequences function is an essential foundation to gaining a full understanding of how biological systems work and how they malfunction. The significance of this understanding will certainly be immense—in part because it will include a vastly deeper understanding of disease processes. This understanding will lead to better disease diagnosis, prevention, and treatment.

■ Elbert Branscomb is associate director of Biosciences.

Mining Genomes



Bioinformatics scientist Ivan Ovcharenko (left) works closely with biologists Lisa Stubbs (center) and Gabriela Loots (right).

Livermore computational tools are helping researchers worldwide understand how genes are regulated.

THE completion of the Human Genome Project in 2003 marked the most ambitious research effort in the history of life sciences: the sequencing of human DNA. However, the project, which included the participation of Lawrence Livermore biologists and computational scientists, was only the first step in understanding life at the molecular level. "The Human Genome Project gave us the sequence of the human DNA but not the manual that explains what it means," says Ivan Ovcharenko, a bioinformatics scientist in Livermore's Computation Directorate.

A significant challenge remains in identifying regulatory elements (REs), which are sequences of DNA that interact with specific proteins to serve as "on–off" switches for genes. REs function in remarkably similar ways in all species, from microbes to humans. However, finding them is particularly challenging in large and complex genomes such as those of mammals. Human REs can be located directly next to the gene they control, or they can be 1-million DNA bases away, buried in a "gene desert." Gene deserts, of particular interest to many biologists, are the large and seemingly barren areas located between genes.

Gene deserts were once considered to have no biological use and were dismissed as "junk DNA." (See the box below.) However, researchers at Lawrence Livermore and Lawrence Berkeley national laboratories and the Department of Energy's Joint Genome Institute (JGI) have shown that gene deserts contain large numbers of REs. Medical and

A Short Genome Primer

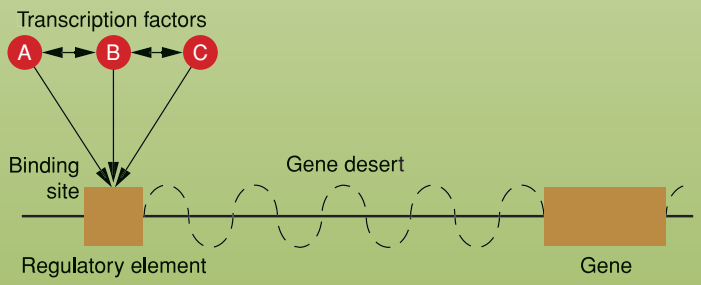
The genome is an organism's complete set of DNA. Genomes vary widely in size: the smallest known genome for a bacterium contains about 600,000 DNA base pairs, while human and mouse genomes have some 3 billion base pairs, equivalent to 3 gigabytes of information. Except for mature red blood cells, all human cells contain a complete genome. Each cell contains 23 pairs of chromosomes in their nuclei, and each chromosome contains two tightly coiled strands of DNA (deoxyribonucleic acid). A DNA strand is an extremely long polymer composed of sequences of nucleotides—the four chemical bases of adenine, cytosine, guanine, and thymine, commonly abbreviated as A, C, G, and T. These chemical bases are attached to a sugar–phosphate chain. The DNA sequence is the particular side-by-side arrangement of bases along the DNA strand (for example, ATTCCGGA).

Certain sequences of letters constitute genes, which are responsible for making proteins. Genes differ only in their sequence of DNA bases. Surprisingly, the 30,000 genes (each about 3,000 letters long) that have been identified through the Human Genome Project comprise only 2 percent of the human genome. About 45 percent of the genome is repetitive DNA that has accumulated over millions of years of evolution and seems to serve no function.

The remaining 53 percent of the genome is noncoding, nonrepetitive DNA, the function of which is still unclear. Part of the noncoding DNA is composed of so-called gene deserts, long stretches of sequences without any protein-coding genes. These gene deserts can stretch more than 5 million bases in length between genes. Some deserts are home to regulatory elements (REs), which are sequences of DNA about 200 letters long and are involved in turning genes "on" and "off." REs combine with transcription factors, which are small proteins, at specific binding sites. When this happens, the DNA strand unravels so that the RE–transcription factor complex abuts the gene it regulates, causing the gene to begin the process for making a certain protein.

A few institutions, including Lawrence Livermore and Lawrence Berkeley national laboratories, are leading the scientific efforts to study REs and determine their role in gene activity and disease. In 2003, a team of researchers from Lawrence Berkeley and the Department of Energy's Joint Genome Institute (JGI) compared DNA sequences from gene deserts in the human, mice, frog, and fish genomes and discovered sequences that regulate genes over surprisingly long distances. "Gene deserts may not be home to any genes, but they can host DNA sequences that act as long-distance switches to activate far away genes," says JGI Director Edward Rubin, who led this research. One of the coresearchers of this pioneering work was bioinformaticist Ivan Ovcharenko, who is now at Livermore.

"It appears that one RE can affect several genes, and one gene can have many REs," says Livermore biologist Gabriela Loots. "We're at the frontier of a new field." In time, scientists may also discover other important sequences in gene deserts.



Regulatory elements are found along vast stretches of gene deserts. They combine with transcription factors to regulate protein-coding genes.

biological researchers can learn important information about the origins and mechanisms of disease, including heart disease, cancer, and AIDS, from studying the functions of REs in these vast desert regions.

"Although REs exist as oases of function in deserts of nonfunction," says Ovcharenko, "it isn't clear how to reliably identify REs because they have no real signature." In an effort to help researchers locate REs in published genome sequences of many different species, Ovcharenko and colleagues have developed a suite of analytical and visualization computational tools. (See the box on p. 8.) The tools are part of Livermore's virtual Comparative Genomics Center, and researchers worldwide can access them online at www.dcode.org. The tool development team includes Ovcharenko, biologists Lisa Stubbs and Gabriela Loots of Livermore, Marcelo Nobrega of Lawrence Berkeley, and Ross Hardison and Webb Miller of Pennsylvania State University.

"Ivan is at the computational end, creating new methods and tools to tackle critical problems in genome biology," says Stubbs. "We provide the biological expertise to test their reliability and usefulness. After Ivan's programs make a set of predictions, we test those predictions in the laboratory to study RE function in live cells or in animals. (See *S&TR,* April 2005, pp. 20–22.) Ivan, in turn, takes our experimental results and refines his programs to enhance their performance."

"While the tools aren't 100 percent accurate, they are a significant advance that allows us to expedite our genomic research," says Loots. "Instead of going on a hunting expedition, we use the tools to zero in on stretches of DNA that offer the most potential."

Genome Data Growing Fast

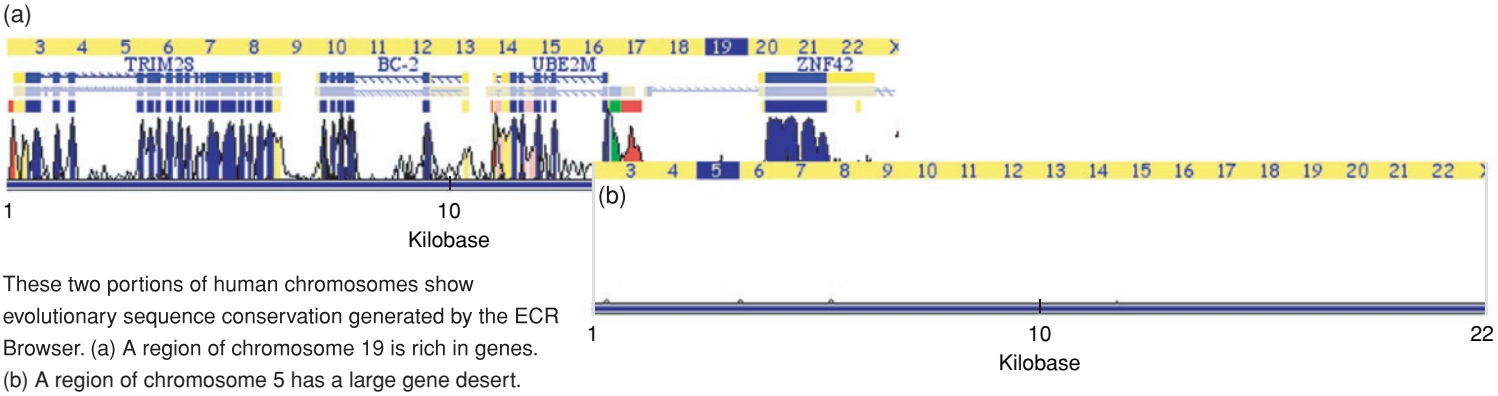
The Livermore suite of computational tools has become popular because of the rapidly growing body of sequenced genomes being generated in the public domain. "Biologists need fast and reliable methods and tools to efficiently analyze the massive amount of data emanating from public sequencing efforts," says Ovcharenko. For example, the sequencing of the chicken genome was completed last year, in an international effort involving Stubbs and her group at Livermore, and Susan Lucas and her group at JGI. The two groups sequenced portions of chromosome 11 and all of chromosome 28 in both domestic and wild chickens. The chicken genome sequence is important to biologists because of the animal's prominent role in agriculture, its major role as an experimental model for vertebrate development, and the strategic evolutionary position of birds between mammals and fish.

The computational tools are Web accessible and can be easily used by researchers who have minimal or no computer training. As a result, some 300 international users, with interests ranging from ecology to agriculture to clinical medicine, use the Livermore tools every day.

The team also strives to make it easier for users to visualize their results. "It's difficult to comprehend the meaning of millions of ordered letters, so we've created graphical interfaces to make visual sense of all the information," says Ovcharenko. For example, some programs generate phylogenetic trees that clearly depict the evolutionary relationship between species over millions of years and when one species likely diverged from another. The Livermore programs offer more than static electronic files of the results; they also provide dynamic and interactive data analysis.

"Researchers can walk into my laboratory one day and be using these tools productively the next," says Stubbs. "The Livermore tools have put powerful predictive methods into the hands of the people with the right scientific questions, and this capability has greatly accelerated the pace of discovery."

The tools align and analyze stretches of DNA or even entire genomes of species to find sequences of nucleotides—the four chemical bases of adenine (A), cytosine (C), guanine (G), and thymine (T)—that match exactly or have strong similarities.



These two portions of human chromosomes show evolutionary sequence conservation generated by the ECR Browser. (a) A region of chromosome 19 is rich in genes. (b) A region of chromosome 5 has a large gene desert.

These similar stretches are called evolutionary conserved regions (ECRs) because they represent areas of DNA that have mutated at much slower rates than the rest of the genome over tens and sometimes hundreds of millions of years. The strategy of comparing DNA from different species is called comparative genomics. Livermore researchers have used comparative genomics for several years to identify shared "core" functional elements that define fundamental properties, as well as genes and REs, of different species.

Comparisons between distantly related organisms, such as primates and fish, uncover the fundamental genomic building blocks—protein-coding genes and REs—that are shared by all vertebrates. Comparisons between more closely related species, such as mice and rats, can highlight genes and REs that are changing rapidly and define species-specific functions. This approach is particularly useful, for example, when studying human diseases that do not afflict other species. When mouse and human genomes are compared, about 40 percent of the two genomes are similar; when human and ape genomes are compared, more than 95 percent of the genomes are similar. In contrast, the sequences of humans and fish have diverged so significantly that only about 5 percent of those genomes are obviously related.

Suite of Programs

The Livermore suite of DNA sequence-alignment programs includes zPicture, Mulan, and the ECR Browser: zPicture compares sequences of two species; Mulan compares sequences of multiple species; and ECR Browser compares complete genomes of many species.

The zPicture tool analyzes a chosen part of two species' genomes to identify ECRs. This tool is often used to compare nonvertebrate genomes, including those of microbes. Ovcharenko designed the genome alignment visualization so that the reference DNA sequence is linear along the horizontal axis and the percentage of similarity is plotted along the vertical axis. This arrangement provides an immediate visual annotation of candidate REs found in genomic sequences up to 1 million bases long.

Mulan goes a step further than zPicture by aligning sequences from multiple species. Mulan determines the phylogenetic relationships among species and generates phylogenetic trees. It also provides detailed overviews of sequences, constructs DNA alignments in both graphic and textual formats, and presents users with several visual display options. The speed with which Mulan handles genomic sequences of millions of bases and the dynamic character of the user interface are unique among genomic tools.

The Livermore team illustrated the power of Mulan when the program analyzed the GATA3 gene and identified its potential REs. GATA3 is one of the key genes involved in the formation of bones, hair, and teeth. The team found that the gene was conserved among humans,

```
Human   GTGTATTgAACAaTaaGAGATAATAATCTAttaaCATTgTCaTcaCGTtGcGtTtTgCTC
        ||||||| ||||| | ||||||||||||||||    |||| || |  ||| | | | | |||
Mouse   GTGTATTtAACAcT--GAGATAATAATCTAaggcCATTtTCtTggCGT-GtGaTgTcCTC

Human   TGCCCtTcCaGacaTCTctACATGgAtGCCATaaGCTCtT-TCtTCTTATCTAGGTGTTg
        ||||| | | |   |||  ||||| | |||||  ||||| | || ||||||||||||||||
Mouse   TGCCCaTaCtG-tgTCTgcACATGtAaGCCATggGCTCcTgTCcTCTTATCTAGGTGTTt
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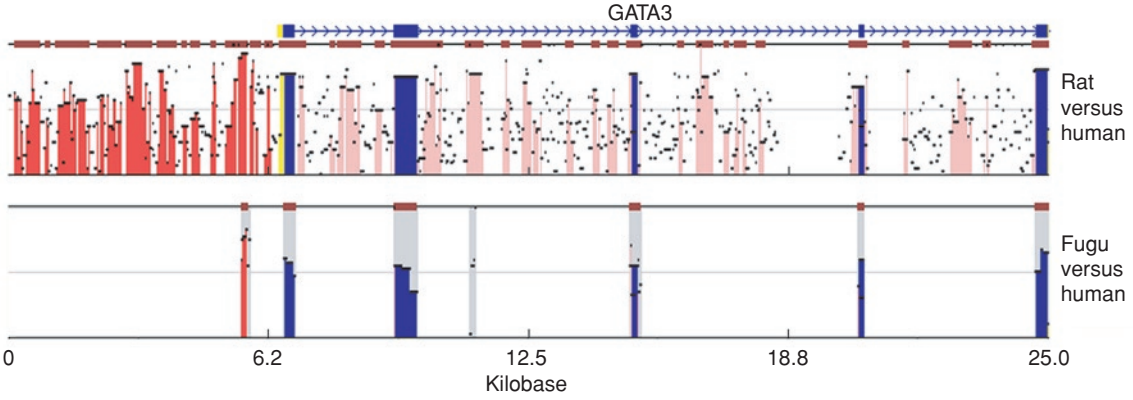
Biologists use a suite of computational tools for aligning and analyzing stretches of DNA to compare sequences of nucleotides (the four chemical bases commonly abbreviated as A, C, G, and T). In this comparison of human and mouse genomes, the lower-case letters indicate mismatches; upper-case letters indicate those that match exactly or have strong similarities.



Analysis of the human, rat, and fugu (a Japanese pufferfish) GATA3 gene using the zPicture DNA sequence-alignment program shows much greater similarities in the DNA between rat and human than between fugu and human. Blue corresponds to the gene, and light red and dark red indicate noncoding DNA.

rodents, birds, amphibians, and fish, a group of species that span 450 million years of evolution.

The team also found five candidate REs that may regulate GATA3. One of them is present in all species, suggesting this RE plays a key role in GATA3. Three of the other REs are present in the human, rodent, and chicken genomes but are not detected in the frog and fish genomes. "One could speculate that the key involvement of the GATA3 gene in the growth of hair and feathers might be regulated by one of these three REs, and that their absence from the frog and fish genomes may be linked to the

Marrying Computer Science and Biology

Finding regulatory elements on vast stretches of gene deserts would be impossible without sophisticated computer programs. The suite of programs developed by Ivan Ovcharenko and other Livermore researchers is indicative of the growing marriage between bioscience and computer science.

Peg Folta, division leader of Computer Applications Research for Energy, Environment, and Biological Computations, points out that computer scientists partnering with the Biosciences Directorate increasingly have a strong understanding of biology. "The blend of disciplines is becoming more commonplace, and we think it represents the future of biological research," she says.

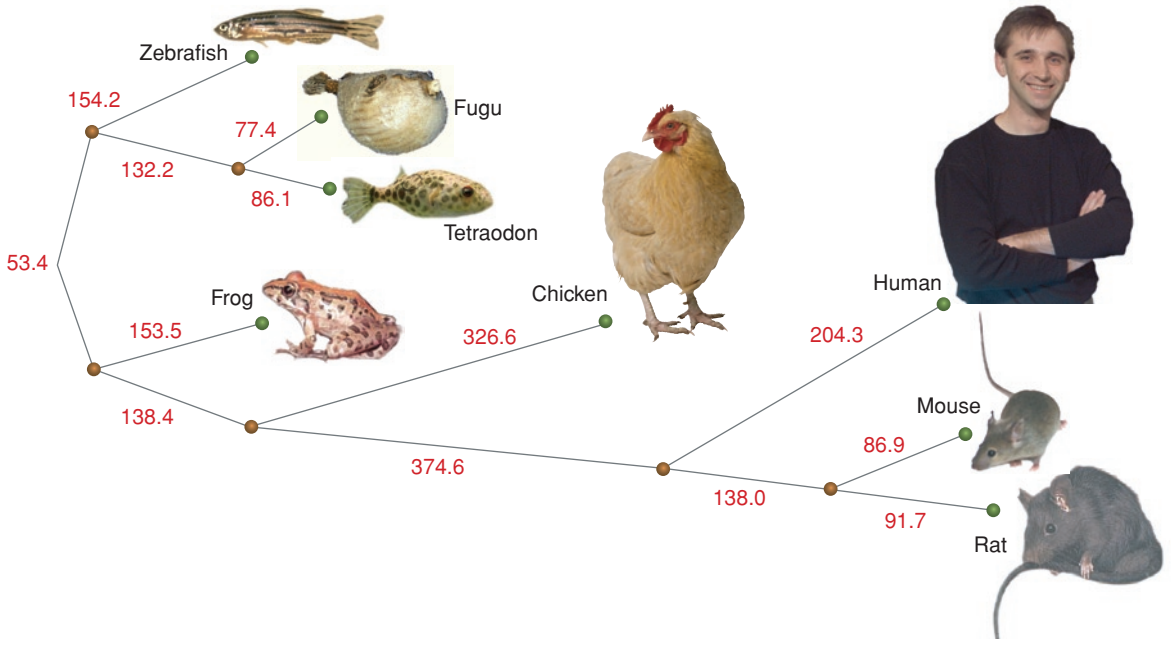
Folta notes that computer science has been applied to the field of physics for many years. As a result, the field of computational physics is mature. However, this is not the case in computational biology. Until recently, the merging of the biology and computation fields was largely happenstance. A few computational scientists learned biology on their own to make important contributions, and a few biologists became computer savvy and learned to develop software and use computers to aid their research.

Applying computational science to biological challenges has matured in the past decade, especially with the completion of the Human Genome Project in 2003 and the resulting onslaught of information. The project would have been impossible to complete without powerful computers and specialized software. An increasing number of colleges offer both undergraduate and graduate degrees in computational biology or bioinformatics. Computational biologists analyze biological activity of living organisms, including protein–protein interactions, protein structures, and signaling networks using computational methods. Bioinformaticists decode the content encrypted into genomes, developing algorithms and tools to access, mine, and display genome information.

Folta cites a "closed loop" that currently characterizes much biological research: Biologists conduct laboratory experiments, and computer scientists analyze the resulting data by accessing online databases, developing specialized software, and generating models and simulations that give insight to the biologist to design new laboratory experiments. With each loop, the computational methods and software are refined and biological discovery increases.

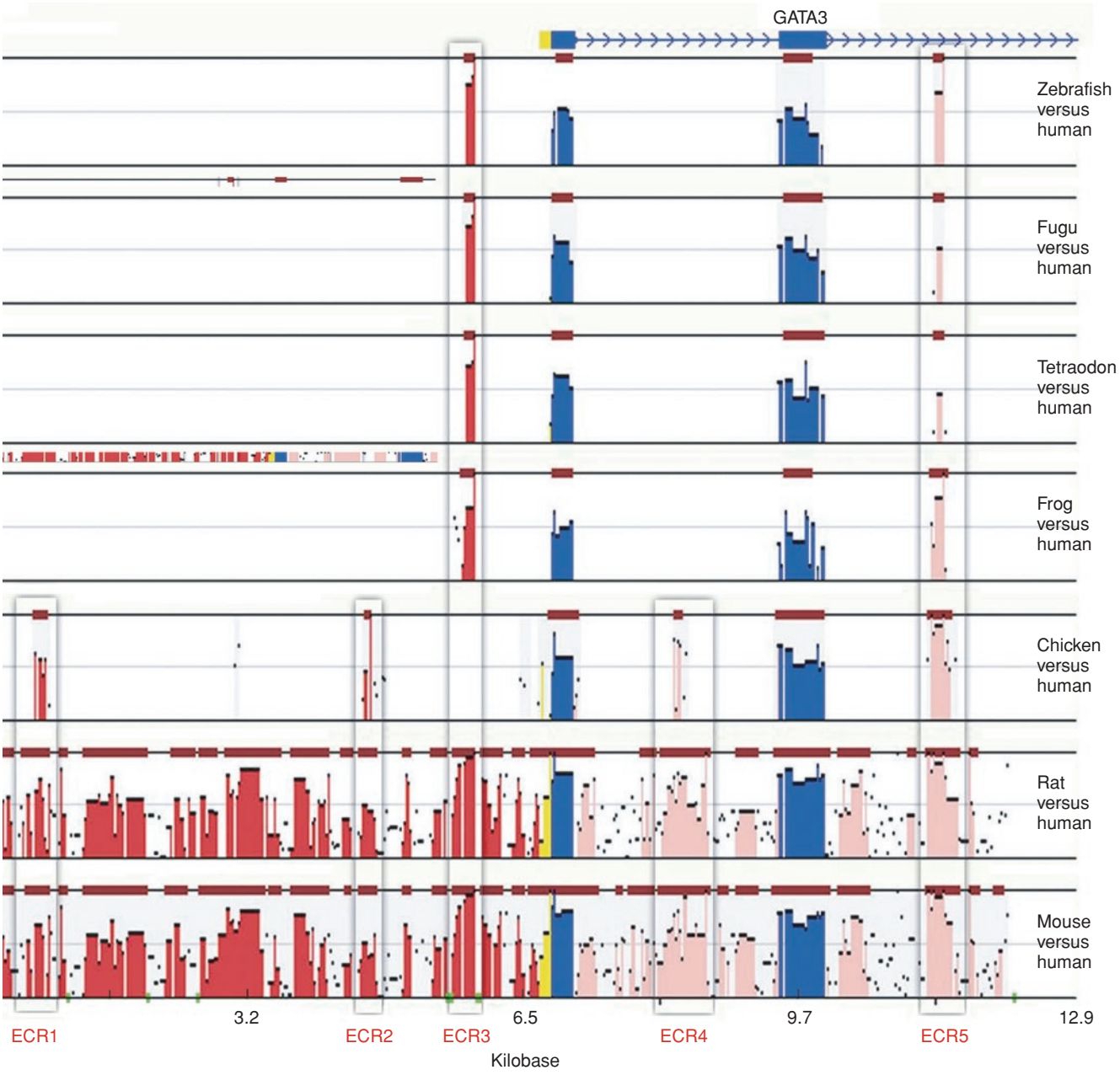
Of the 35 computer scientists who work in Livermore's Biosciences Directorate, one group works alongside biologists, a second works in biodefense research led by the Laboratory's Nonproliferation, Arms Control, and International Security Directorate, and a third is located at the Department of Energy's Joint Genome Institute in Walnut Creek, California.

The Mulan program can generate a phylogenetic tree that depicts the evolutionary relationships between species based on the similarities of their genomes. The red circles represent common ancestors, and the numbers represent nucleotide substitutions per 1 kilobase of genomic sequence.



lack of hair in these species," says Ovcharenko. More interesting, however, was the team's discovery that one RE, called ECR3, is present in all species' genomes except chicken. The team hypothesized that the deletion of this RE many millions of years ago caused the GATA3 gene to function differently in birds, resulting in the hollow bones that make flight possible.

ECR Browser, the most popular of the Livermore online tools, expands the boundaries of alignment to genome scale for comparing vertebrates, invertebrates, and microbes. While offering all the



The Mulan program can align and analyze DNA sequences from multiple species simultaneously. Here, Mulan was used to analyze the GATA3 gene in six species. The program identified five candidate regulatory elements (REs) for the GATA3 gene, which are shadowed in the plot. One RE, called ECR3, is present in all the species' genomes except chicken. It is possible that the deletion of this RE many millions of years ago caused the GATA3 gene to function differently in birds, resulting in the hollow bones that make flight possible.

capabilities of zPicture and Mulan, it also can be used to identify conserved single nucleotide polymorphism (SNP), which is a one-nucleotide genetic change that has appeared in recent evolutionary time (last few thousands of years) and has been found to result in disease or susceptibility to a disease. This ability to identify conserved SNPs is important to medical researchers attempting to identify causes of genetic diseases. Ovcharenko has used ECR Browser to analyze the genomes of human, dog, mouse, rat, chicken, frog, three fish, six fruit flies, and six bacterial species, including *Escherichia coli* and *Yersinia pestis*, the organism that causes plague. ECR Browser is particularly useful for comparing the genomes of bacteria, of which more than 100 have been completely sequenced.

Comparing Apples and Apples

Comparative genomics works best when comparing "apples to oranges," that is, critical genes and REs that are conserved in genomes of distantly related species such as humans and mice. However, many functional elements in the human genome are not present in the mouse genome. "Comparative genomics fails when searching for functional elements in closely related species or comparing apples and apples," says Loots. "Everything seems to be perfectly well conserved, including elements that are functionally important and those that are not. How can we identify functional elements in comparisons of humans and chimps, whose genomes are more than 98 percent identical? From a practical viewpoint, how can we study primate-specific diseases using comparative genomics?"

Phylogenetic shadowing, a method proposed by Eddy Rubin from Lawrence Berkeley and redefined and implemented by the Livermore team in the eShadow program, provides a better tool for studying closely related species. Phylogenetic shadowing is a statistical method that detects and identifies recently or rapidly evolving ECRs. The program is especially useful for understanding the origin of human-specific genetic diseases.

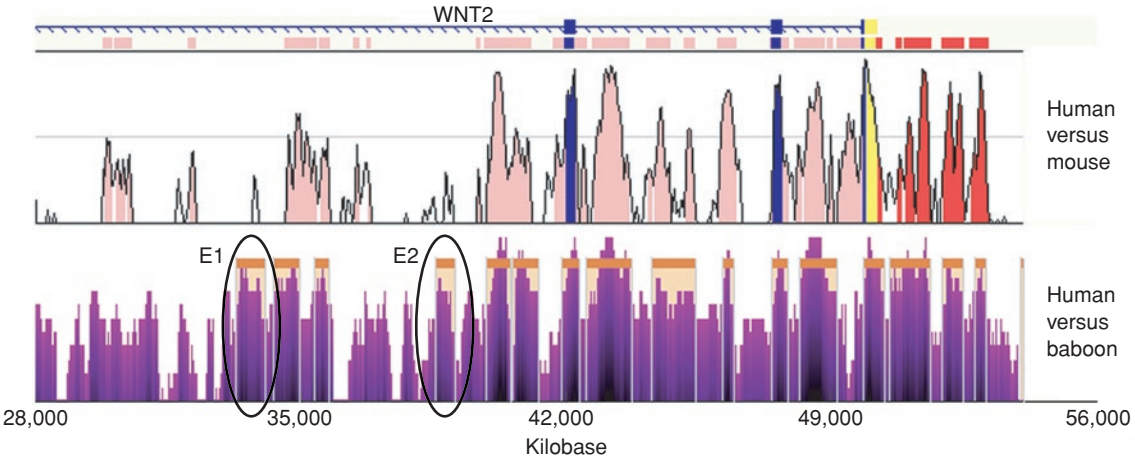
The Livermore researchers used eShadow to study WNT2, an important human gene known to be involved in the early stages of cancer and associated with autism and embryonic development. They found two REs that are highly conserved in humans and baboons but that have diverged in mice. The researchers confirmed the REs' function in the laboratory and found that both reduce the activity of the WNT2 gene. This discovery suggests that the WNT2 REs are conserved in all species, but that different species might use additional elements to modulate the activity of this gene in some organs.

Characterizing Regulatory Elements

The Livermore comparative genomics toolkit also contains programs to characterize important features of REs and to predict their regulatory activities. Two programs, rVista and multiTF, work with zPicture and Mulan, respectively, to detect evolutionary conserved binding sites for proteins called transcription factors (TFs), which interact with REs. About 10 percent of genes in all species encode TF proteins, yielding at least 2,000 different TF proteins in mammals and about 300 TF proteins in bacteria. TFs combine together and bind to REs at transcription factor binding sites (TFBSs). When a TF complex binds to an RE, the activity of this RE is initiated, and the corresponding gene is switched "on" or "off." Because of the sheer numbers of TFs and their combinatorial action, the variety of protein complexes that can be deployed for gene regulation in any species is enormous. Identifying TFBSs on specific REs is a major challenge and one that is attracting much attention from the bioinformatics community. rVista and multiTF are among the most widely used tools for locating TFBSs.

SynoR, the tool most recently developed by the Livermore team, searches for synonymous gene regulators or groups of REs that share similar gene regulation duties, which often bind to similar TF proteins. When a user inputs a combination of TFBSs, the program scans a genome to find the related REs. The team believes this new tool will be especially useful for establishing links between human diseases and REs. "SynoR has allowed us to make observations that suggest understanding regulation of a particular group of genes could be used to help patients with various immunodeficiencies ranging from inherited syndromes to AIDS," says Ovcharenko.

The interconnection of the Livermore programs with other DNA sequence analysis tools creates a unique portal for studying genomes. For example, some tools are interconnected with the Genome Alignment and Annotation (GALA) database at Pennsylvania State University. Once a region of interest has been found in GALA, a user may examine it using the Mulan tool. Likewise, users can access GALA to find additional information about ECRs found by Mulan. Some Livermore tools also connect to the University of



The eShadow program is particularly useful for determining differences among closely related species. This comparison of the human WNT2 gene with mouse and baboon shows E1 and E2 regulatory elements (circled) that are specific to human and baboon.

California at Santa Cruz's Genome Browser, which includes the completed, annotated genomes of many species and links to other genomic resources.

Refinements Continue

Ovcharenko is refining the tools to improve their power and utility. Because of the programs' growing popularity, he is planning to adapt the programs, in particular ECR Browser, so they will work on supercomputers.

More scientists worldwide are beginning to research gene deserts and REs. The potential payoff is a more complete understanding of how a cell functions and species have evolved and greater insight into diseases and their possible cures.

—Arnie Heller

Key Words: Comparative Genomics Center, DNA, ECR Browser, eShadow, evolutionary conserved region (ECR), gene desert, Human Genome Project, Joint Genome Institute (JGI), Mulan, multiTF, regulatory element (RE), rVista, SynoR, transcription factor binding site (TFBS), zPicture.

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Shedding Light on Quantum Physics

Einstein's explanation of Planck's quantum hypothesis is the bedrock of Livermore laser research.

IN a letter to fellow scientist Robert Hooke in 1676, Isaac Newton wrote: "If I have seen farther than others, it is because I was standing on the shoulders of giants." The giants to whom Newton was referring were Copernicus, Brahe, Galileo, and Kepler.

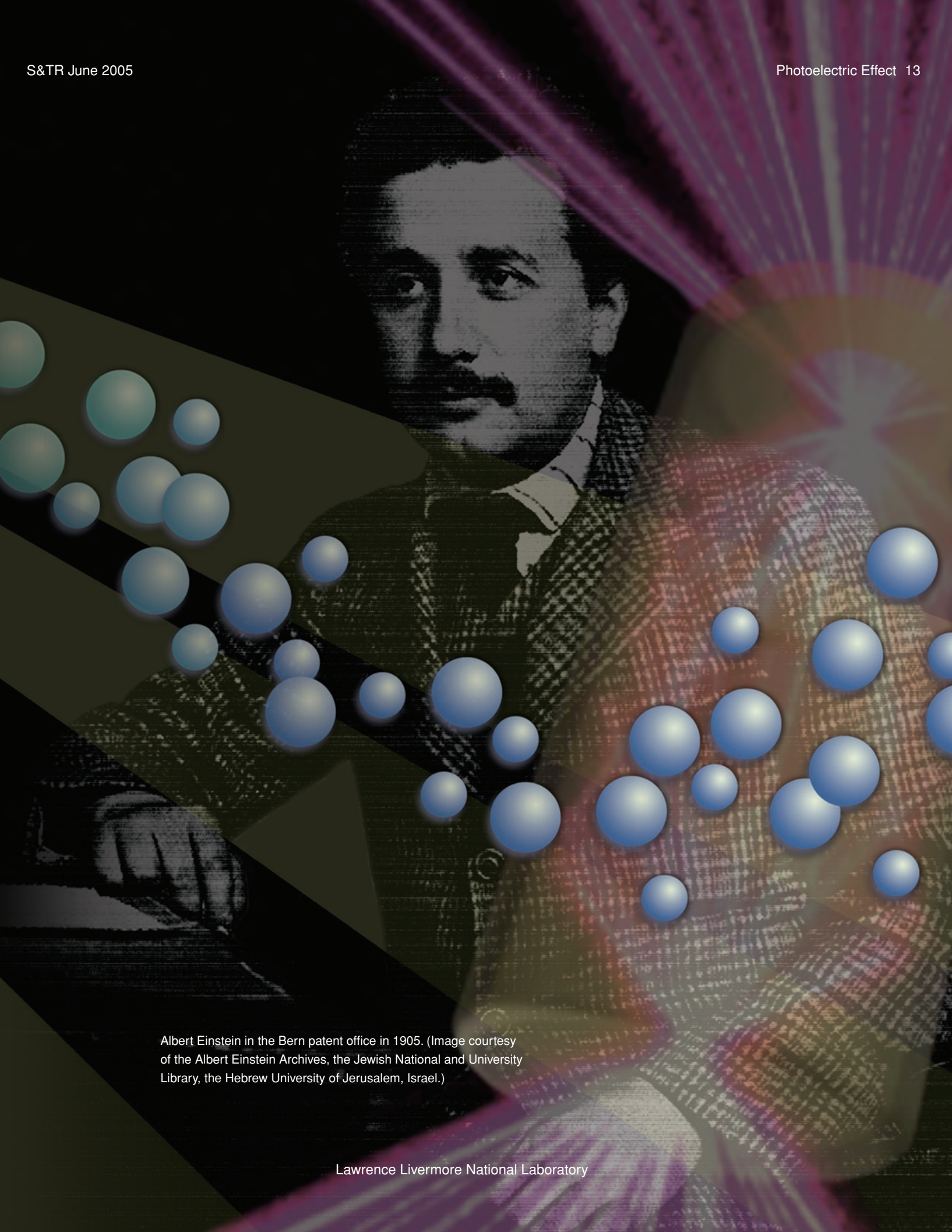
A host of Livermore scientists whose work delves into the nature of light and energy could very well claim to be standing on the shoulders of the 20th century's own physics giant: Albert Einstein.

Livermore physicists using x-ray lasers and single-photon counting experiments to probe the mysteries of materials behavior and biological processes base their work on the tenets underlying two papers published by Einstein early in the last century. In one, Einstein put forth a theoretical explanation of light as a stream of particles. In the other, he explained how radiation is absorbed and emitted by atoms.

Understanding Light as Packets

In March 1905, Einstein submitted a paper entitled "Concerning an Heuristic Point of View toward the Emission and Transmission of Light" to the German journal *Annalen der Physik*. The paper was the first of a series of papers Einstein published that year that ushered in the era of modern physics. In this paper, Einstein resolved several mysterious properties of visible electromagnetic radiation, or light, by proposing that such radiation is quantized; that is, it is emitted from radiating objects in discrete packets. As might be expected, Einstein's novel explanation was so unanticipated that it took more than 10 years to be accepted by the physics community. It wasn't until 1921 that Einstein was awarded the Nobel Prize for his work in this area.

Einstein had been fascinated by the nature of light and electromagnetic radiation for years before the publication of his paper in 1905. Much of the work driving the development of physics in the late 19th and early 20th centuries concerned understanding the nature of light. In 1704, Newton published his book *Opticks*, in which he argued that light was composed of particles. However, by the end of the 19th century, James Maxwell's work on electromagnetic radiation had demonstrated that light and all other forms of such radiation were best explained as waves. At the beginning of the 20th century, a few properties of electromagnetic radiation had yet to



Albert Einstein in the Bern patent office in 1905. (Image courtesy of the Albert Einstein Archives, the Jewish National and University Library, the Hebrew University of Jerusalem, Israel.)

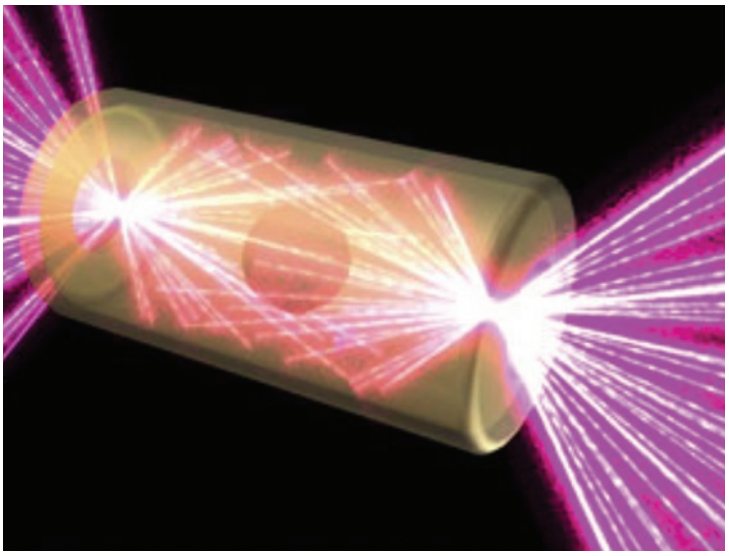
be explained, and these were the puzzles that Einstein set out to unravel.

Planck's Mathematical Trick

One experimental puzzle of electromagnetic radiation that physicists encountered at the turn of the 20th century was so-called blackbody radiation. An ideal blackbody absorbs all radiation to which it is exposed and reflects none, so it appears black to the observer. The absorbed energy, however, is re-emitted to maintain thermal equilibrium. It is the spectrum of this radiation that Einstein ultimately correctly explained.

The puzzling issue was determining the distribution of frequencies of the radiation from a blackbody. That is, predicting the intensity of radiation emitted by a blackbody at a specific wavelength. The classical approach, using Maxwell's equations and conventional thermodynamics, leads to predictions that do not coincide with experimental data at the shorter wavelength end of the distribution.

In 1900, German physicist Max Planck calculated the observed distribution of radiation energy in blackbodies based on the assumption that the oscillating atoms in the walls of the blackbody do not emit radiation at all energies—only at highly prescribed values. This assumption leads to a very different, and correct, expression for the distribution of radiation energy in a blackbody. Planck's assumption was based on a theory about the properties of atomic oscillations—not about the true nature of light. In solving another puzzle about electromagnetic radiation (see p. 15), Einstein later realized that light itself was quantized.

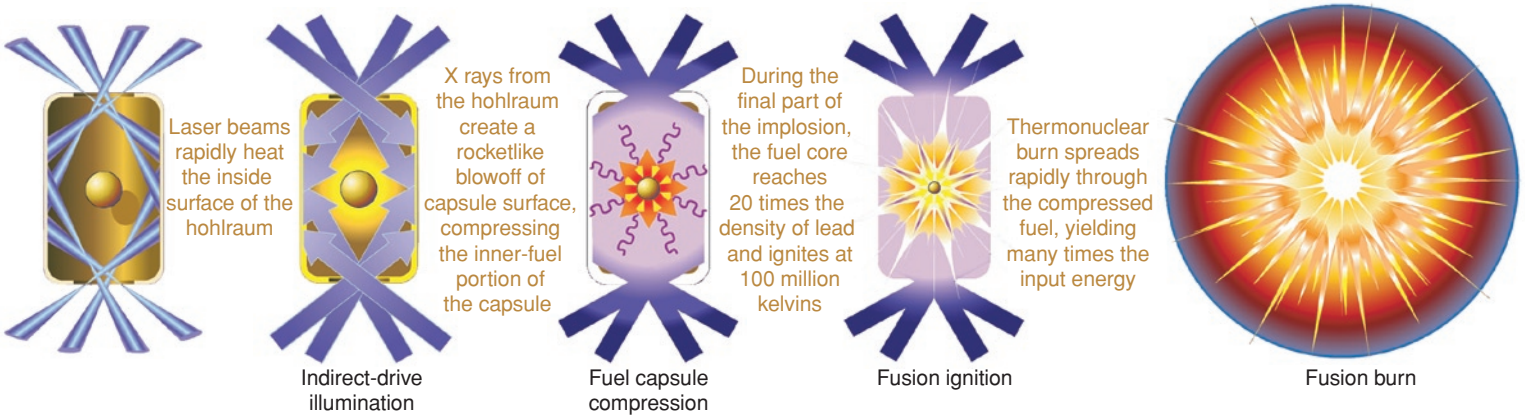


An artist's rendering shows how laser beams deposit their energy on the inside surface of a metal cylinder or "hohlraum," where the energy is converted to thermal x rays. The x rays heat and ablate the plastic or metal surface of the ignition capsule, causing a rocketlike pressure on the capsule, which forces it to implode.

The Photoelectric Effect

By 1905, Einstein was at the University of Zürich finishing his doctoral thesis in which he used statistical mechanics (the study of the motion of objects using mathematical tools for dealing with large numbers of objects) to infer the size of molecules. With his mathematical skills and fascination with light, Einstein had a breakthrough insight: Planck's explanation made perfect sense if the radiation in a blackbody was a collection of discrete light particles, which he called quanta.

In the paper he submitted to *Annalen der Physik*, Einstein explained that Planck's



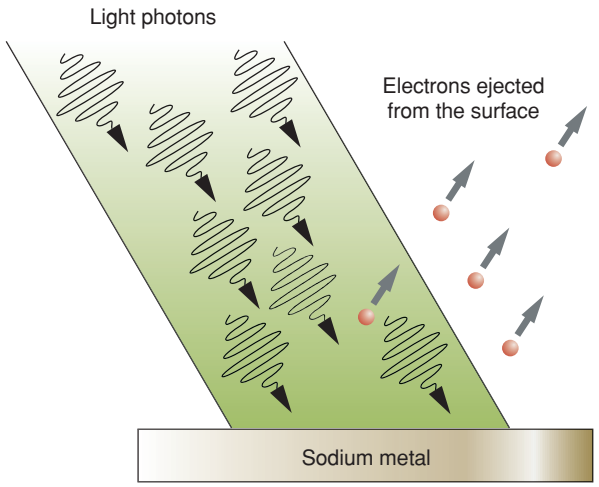
The steps of an inertial confinement fusion reaction, in which more energy is produced than is used to initiate ignition. Under laboratory conditions, the sequence produces energy gain equivalent to the power of a miniature star, lasting for less than a billionth of a second.

mathematical result in fact provided the true characterization of light. He then used this insight to explain what was then considered an unrelated puzzle: the photoelectric effect.

The photoelectric effect was first observed by Heinrich Hertz in 1887 and refers to the emission of electrons from the surface of a metal in response to incident light. When light is shone on certain metals, energy within that light is absorbed by electrons within the metals. This absorbed energy can cause the electrons to be photoionized, or ejected, from the surface of the metal.

The number of electrons ejected is proportional to the intensity of the light. This behavior is consistent with light being a quantum or a wave phenomenon. The energy of the ejected electron is proportional to the frequency of the light. However, if the frequency of the light drops below a certain threshold known as the work function (which is different for each metal), no electrons are ejected. For example, blue light causes sodium to release electrons, but red light does not. This property of the photoelectric effect could not be explained by characterizing light as a wave.

Einstein explained all aspects of the photoelectric effect with his light-quanta hypothesis in which light acts like small particles. He understood the work function as the amount of energy that the electron needs to be released from the atom. In the photoelectric effect, electrons in the metal absorb light quanta. If the energy of the quanta is greater than the work function, electrons are ejected. But if the energy is less than the work function, electrons cannot leave the metal, regardless of the number of quanta available.



A diagram of the photoelectric effect shows that light behaves like particles. The details of the photoelectric effect were in direct contradiction to well-developed classical physics. The explanation marked one of the major steps toward quantum theory.

Blackbodies and Fusion

Blackbodies are crucial for experiments performed at Livermore involving inertial confinement fusion, the process of compressing and heating hydrogen isotopes until they fuse together, releasing enormous amounts of energy. The National Ignition Facility (NIF), scheduled for completion in 2008, will be used to achieve fusion ignition and burn. The facility and associated experimental efforts are the highest profile examples of fusion research at Livermore. (See *S&TR*, September 2003, pp. 4–14.)

A hohlraum serving as a blackbody is the target at which the NIF lasers are pointed. In this case, the hohlraum is a small, gold cylinder approximately 1 centimeter long and half a centimeter in diameter in whose center resides a spherical fusion-fuel capsule. When the hohlraum is hit with 300 trillion watts of laser beam energy, its metal is heated to a high temperature, creating a 3-million-degree x-ray oven. The energy radiating from the hohlraum implodes the capsule and ultimately ignites the fusion fuel (deuterium and tritium), which begins the ignition reaction.

Livermore physicists Mordecai Rosen and Larry Suter, both leading experts on laser hohlraum physics, have been instrumental in the development of the fusion project. “NIF hohlraums can serve as a physics factory in which we study high-energy-density physics, including fusion” says Rosen.

Answering Questions of Radiation

The second Einstein paper, which set the stage for future discovery of the laser, was published in 1917 by *Zeitschrift fur Physik* and entitled “On the Quantum Theory of Radiation.” In this paper, Einstein continued his inquiry into the properties of light and matter with an explanation of how radiation is absorbed and emitted by atoms.

In particular, he described three main processes for how radiation interacts with matter: spontaneous emission, absorption, and stimulated emission. In absorption, an atom absorbs a quantum of radiation and reaches a higher energy state known as an excited state. In stimulated emission, an atom in an excited state decays to a lower energy state by emitting a quantum of radiation; emission is caused by an incident quantum with the same energy as the emitted quantum. In spontaneous emission, an atom in an excited state decays to a lower energy state without an external “catalyst.” These processes are key to understanding how lasers work.

Isolating Single Photons

Livermore scientists Thomas Huser and Chris Hollars of the Chemistry and Materials Science (CMS) Directorate have an everyday appreciation of the implications of both the photoelectric effect and radiation emission. With Laboratory Directed Research and Development (LDRD) Program funding, Huser, a physicist, and Hollars, an

analytical chemist, are applying single-molecule spectroscopy to biophysical measurements. The researchers first attach fluorescent labels to single biomolecules. Then they image the fluorescent biomolecules either on surfaces or diffused in solutions to characterize them and determine their interactions with other molecules of interest.

Imaging requires a laser to excite single photoluminescent molecules located at the focus of a confocal optical microscope. The confocal microscope eliminates much of the background noise that normally comes with a detection technology sensitive enough to identify a single-photon event.

Each photon fluoresced by the molecule is detected by an avalanche photodiode, which is commonly used in this type of research. In the photodiode detector, an incoming photon hits the photodiode lattice material—a mix of indium, gallium, and arsenic—and creates a photoelectron. "This phenomenon is precisely what Einstein was describing," says Huser. That photoelectron, in turn, hits another electron and collides with the atomic lattice, releasing additional electrons via secondary ionization. These resulting electrons also are accelerated, which induces an avalanche of electrons. As a result of this amplification, one photon creates a strong electrical pulse, which constitutes the detection of the photon.

Each molecule can emit only one photon every few nanoseconds, which means that Huser and Hollars are looking at sequences of millions of emitted photons over a period of minutes. A close examination of the precise time that each photon arrives at the detectors can be used to describe the state or behavior of the labeled biomolecule. "After the statistical analysis, we were able to show that we are, indeed, detecting single-fluorescence-

A Long History of Laser Research

The National Ignition Facility (NIF) is the latest project in a long history of laser research at Livermore. "The Laboratory has been building lasers for over 30 years, and the focus of these efforts has evolved to include both defense and scientific applications," says physicist Joe Nilsen.

Physicist Chris Barty cannot put too fine a point on it. "Lasers and Livermore have a big overlap," says Barty. "Livermore is the world leader in at least two aspects of lasers." Barty cites those two aspects as high-energy lasers, such as NIF and Nova, and high-average-power lasers, such as those used in the uranium atomic vapor laser isotope separation (U-AVLIS) process.

Livermore has also led laser research in the areas of high-peak-power lasers and x-ray lasers.

High-Energy Lasers

High-energy lasers are used at Livermore to provide the energy densities required for inertial confinement fusion and to study high-energy-density physics. Typically, these lasers work in short bursts for tens of nanoseconds.

Livermore's successful high-energy Nova laser became operational in December 1984 and at the time was the world's most powerful laser. After 14 years and more than 14,000 experiments, Nova fired its last shot. Nova and a demonstration project, the Beamlet laser, served as the proving ground for Livermore's next-generation high-energy laser project, NIF, the 192-beam facility designed to ultimately achieve thermonuclear ignition.

High-Average-Power Lasers

High-average-power lasers typically provide laser energy with trains of pulses or continuous pulses. In the early 1970s, Livermore's U-AVLIS Program began. This system used copper-vapor and dye lasers and was designed to enrich uranium for nuclear power applications. The system technology also has applications in precision machining, pumping ultrashort-pulse lasers, creating laser displays, and treating skin conditions.

Some of the technologies developed for the U-AVLIS system were also used in 1996 at the University of California's Lick Observatory near San Jose, California, to demonstrate the laser guide star concept in which a laser beam is focused into the upper atmosphere, producing an artificial star to help improve telescope performance. The Livermore team, along with colleagues from the University of California and the California Institute of Technology, later installed adaptive optics and a guide star system on the 10-meter telescope at Keck Observatory in Hawaii. Since the installation, astronomers have been probing the deepest regions of the universe, obtaining astral images with resolution greater than that of other land-based telescopes or even the orbiting Hubble Space Telescope.

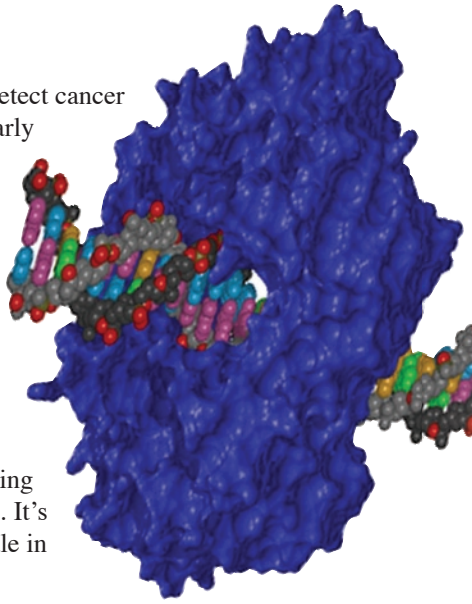
High-Peak-Power Lasers

High-peak-power lasers are devices in which the laser power is packed into a very short pulse—less than a trillionth of a second in duration. These ultrashort pulses allow extremely high energy densities to be achieved in targets. Livermore's high-peak-power Petawatt laser operated for 3 years, until 1999. At full energy of about 680 joules, the shots delivered more than a quadrillion watts (or petawatt, which equals 10^{15} watts) of power, exceeding the entire electrical generating capacity of the U.S. by more than 1,200 times. The Petawatt laser was developed originally to test fast ignition for inertial confinement fusion in the ongoing attempt to ignite a pellet of hydrogen fuel and harness the energy that powers the Sun. The power of the Petawatt also opened up entirely new physical regimes to study. Now, scientists can use lasers, not just particle accelerators, to study high-energy-density physics and the fundamental properties of matter. They may also be

photon events from a single molecule," says Hollars.

Researchers involved in this highly multidisciplinary work combining chemistry, physics, and biology look toward studying single-biomolecule interactions between DNA, proteins, and other gene products. "Many processes have to occur on the molecular level to keep us healthy," says Huser. Hollars and Huser plan to use their experimental capabilities to gain a better understanding of some of these fundamental processes. They envision mostly biomedical applications for single-molecule detection. "In cancer research, we want to detect cancer in a person at a very early stage," says Huser. "The hope is for researchers to develop single-molecule disease markers."

Achieving those goals is certainly a challenge, and Huser points out that the work can be arduous. "Currently, we're looking one molecule at a time. It's like looking for a needle in



Single-photon detection methods are being used to elucidate interactions between biomolecules. This computer illustration depicts the interaction between a clamp protein (blue) and double-stranded DNA.

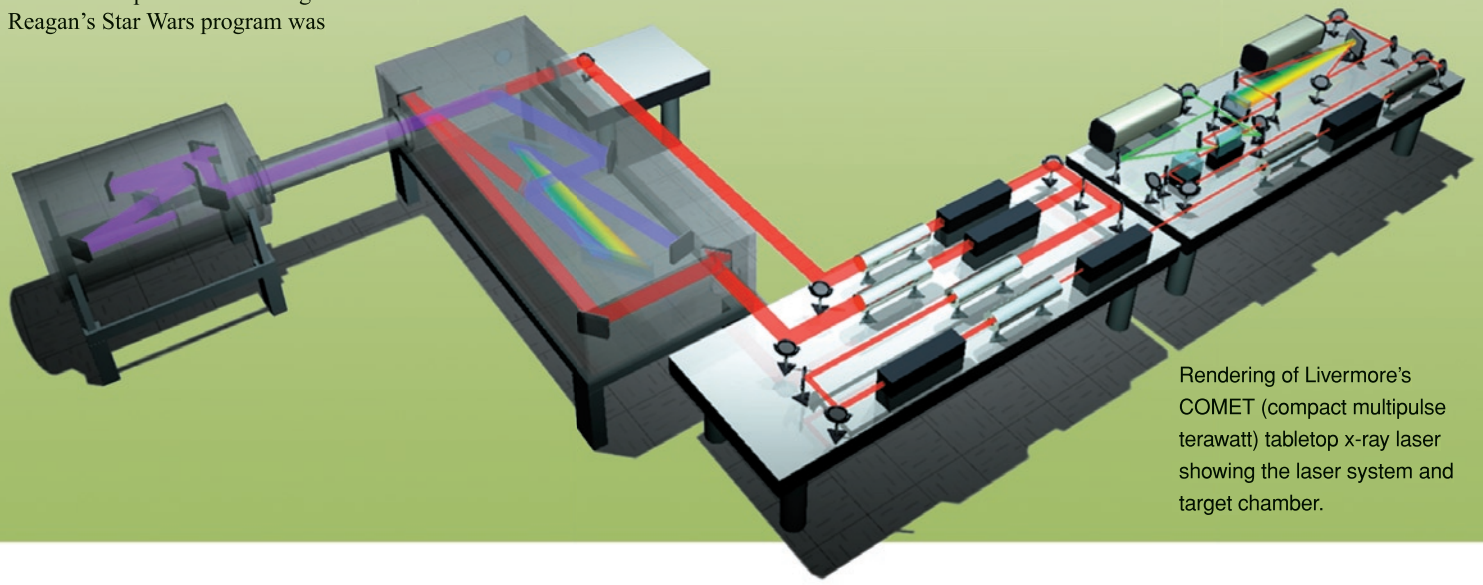
able to re-create in the laboratory the energized plasmas around black holes and neutron stars for astrophysical research.

X-Ray Lasers

X-ray lasers produce coherent x-ray light and can be pumped from either nuclear explosions or from intense optical lasers. The x-ray laser program began in the early 1980s as part of President Reagan's challenge to the scientific community to develop a defense against nuclear-armed ballistic missiles. This challenge led to the launch of the so-called Star Wars program, the Strategic Defense Initiative. In 1984, Novette, the forerunner of the Nova laser, was used for the first laboratory demonstration of an x-ray laser. With this laser, Livermore researchers assumed the role of leading the world in gaining new understanding of the physics of x-ray lasers.

Nilsen explains that although President Reagan's Star Wars program was eventually scaled back and transformed into the National Missile Defense Program, the knowledge gained from the earlier efforts have easily channeled to other research areas such as biotechnology, materials science, and materials analysis.

"The laboratory x-ray laser has become a high-repetition-rate tabletop facility used to develop plasma diagnostics such as interferometers," says Nilsen. "We're measuring the electron density of plasmas, and it is helping us validate our codes for calculating inertial confinement fusion experiments." Nilsen also notes the tremendous technical advances made in x-ray technology over the years. "With a tabletop system, we now do x-ray interferometry without destroying the target or the interferometer. The development of novel x-ray optics has extended many of the sophisticated measurement techniques for optical lasers into the x-ray region."

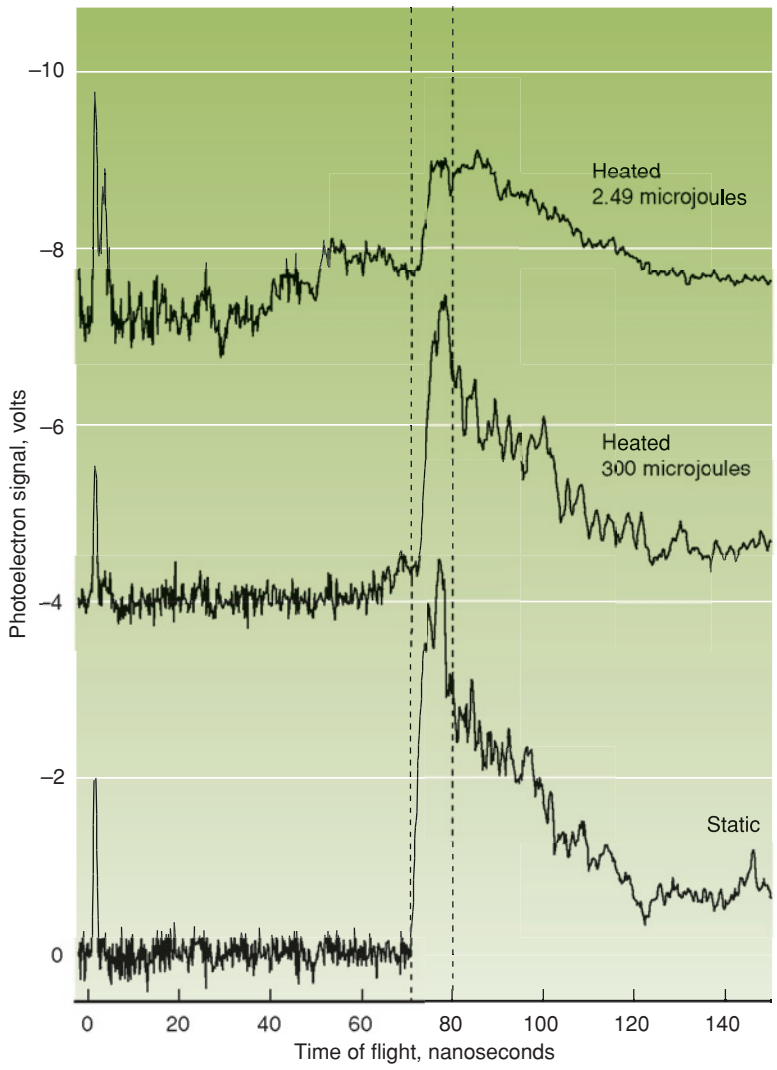


Rendering of Livermore's COMET (compact multipulse terawatt) tabletop x-ray laser showing the laser system and target chamber.

a haystack, but it would be impossible to achieve without Einstein's contributions," says Huser.

Pulling Electrons from Metals

Art Nelson of the CMS Directorate has been using the photoelectric effect to study the properties of solids as they rapidly evolve. Using a technique called x-ray photoelectron spectroscopy (XPS), a metal is exposed to a spectrum of x rays, and the energy distribution of the ejected electrons is measured. Every metal has a unique electronic-structure energy distribution. Studying these distributions—and how they change, for example, when the material is heated—offers scientists insights into the nature of the metal.



Photoelectrons from static and laser-heated ultrathin polycrystalline copper foil are induced using an x-ray laser. The resulting spectra are unique to each element and help scientists better understand the properties and behavior of materials under extreme conditions.

A pulsed monoenergetic x-ray source is required.

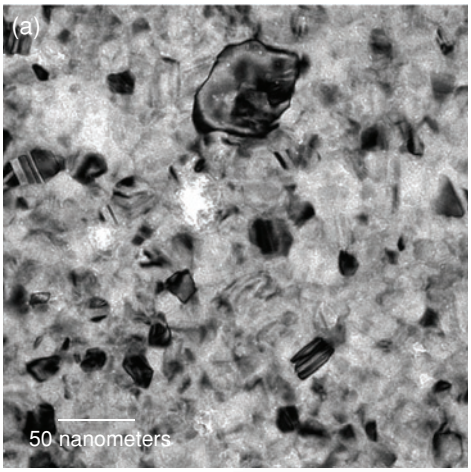
In 2001, Nelson, along with Jim Dunn of the Physics and Advanced Technologies (PAT) Directorate, began to use picosecond x-ray lasers as probes to study materials undergoing rapid changes. (With LDRD funding, PAT had developed a compact x-ray laser source and established an x-ray laser beamline to explore new science applications.) The team uses an optical laser pump and x-ray laser probe to understand the dynamics of a material from picosecond to picosecond.

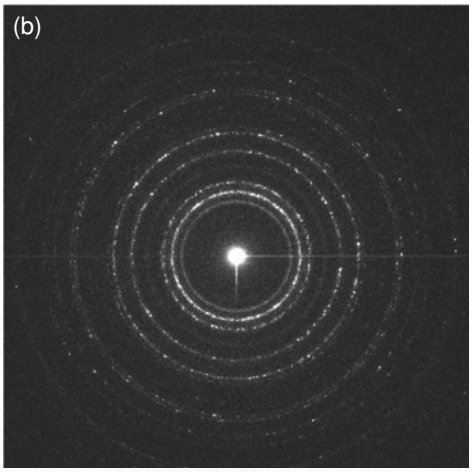
In this technique, the optical-laser pump quickly heats the material producing an excited state or causing a phase transition (for example, melting). The x-ray laser measures the resultant perturbations by probing the state of the material's electrons at various times. "Because the pulse of an x-ray laser is so short," says Nelson, "one can get a snapshot in the picosecond range by analyzing the electrons ejected from the surface of the metal." Such analysis requires directly measuring the kinetic-energy distribution curve of the ejected electrons.

The team's goal is to understand the evolution and processes that occur in a heated material by interpreting the changes in its measured electronic structure.

Dunn and Nelson form one of only a few teams in the U.S. currently working on x-ray laser source development and applications. According to Dunn, the advantage of x-ray lasers over optical lasers is significant in this type of work. The short wavelength and pulse of an x-ray laser make it optimal for looking at materials dynamics. Additionally, x-ray lasers have a high brightness and are directional, which means the beam can be directed to an exact location. Currently,

Nelson and Dunn are using x-ray lasers to study ultrafast laser-heated copper—a material being used for targets in NIF.





Livermore scientists use x-ray lasers as probes to study materials undergoing rapid changes. (a) Transmission electron microscopy is used to create a photomicrograph of ultrathin copper foil. (b) This image shows an electron diffraction pattern of ultrathin copper foil. Understanding the material properties of these copper foils under changing—and extreme—conditions is essential to the Laboratory's use of copper in targets for the National Igniton Facility.

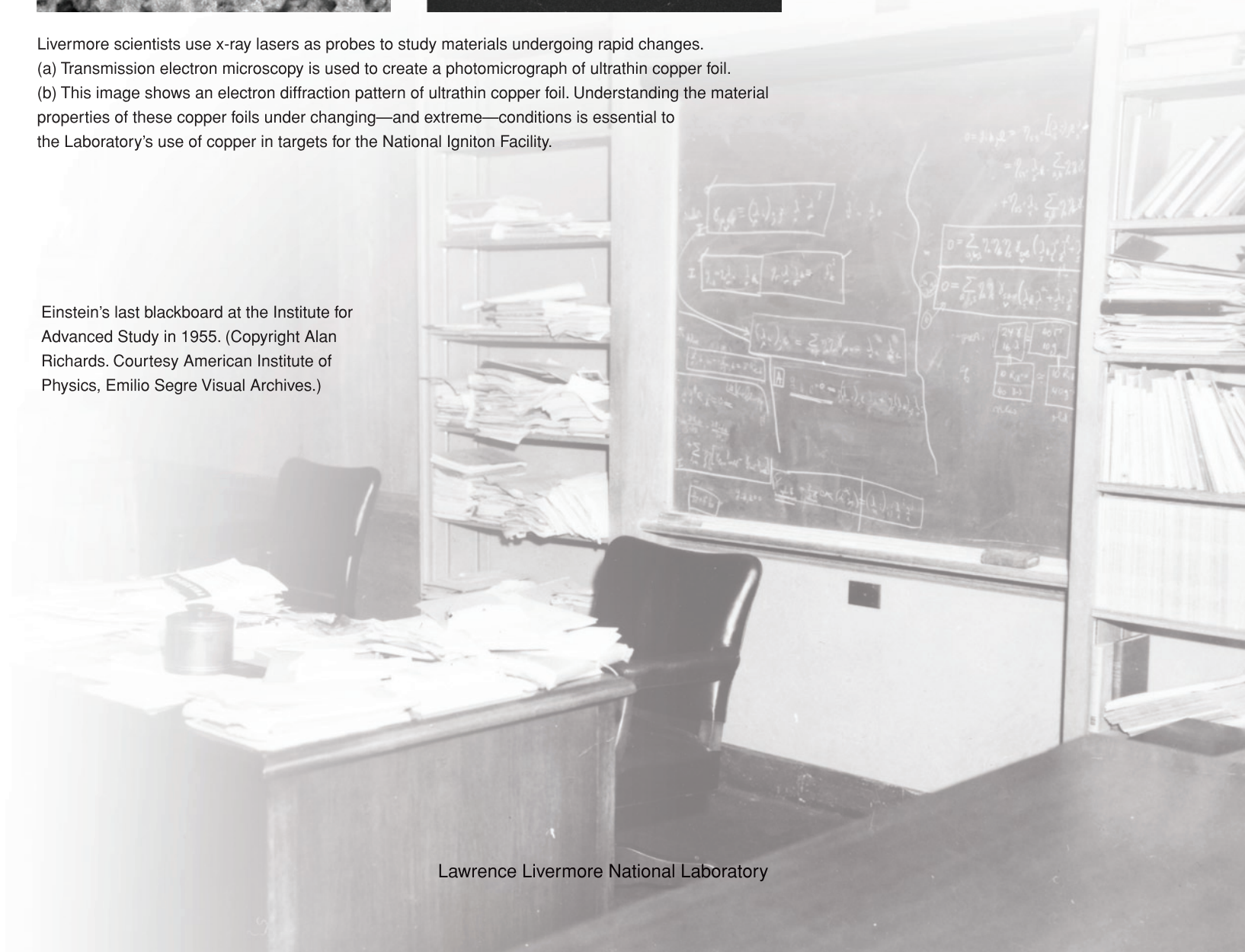
A Silent Appreciation

Livermore physicists and other scientists around the world acknowledge and revere the profound legacy that Einstein's 1905 papers have left us. And when future generations stand on the shoulders of today's physicists, they will see farther because of that legacy.

—Maurina S. Sherman

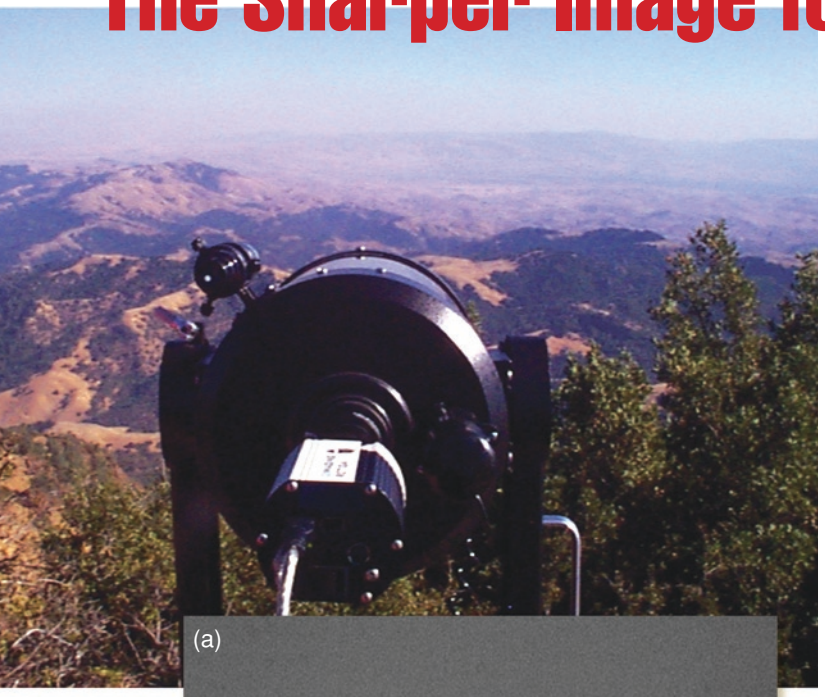
Key Words: Albert Einstein, blackbody radiation, hohlraum, inertial confinement fusion, light quanta, photoelectric effect, photons, quantum mechanics, single-photon detection, x-ray lasers, x-ray photoelectron spectroscopy.

For further information on the Laboratory's celebration of the World Year of Physics, see www.llnl.gov/pao/WYOP.



Einstein's last blackboard at the Institute for Advanced Study in 1955. (Copyright Alan Richards. Courtesy American Institute of Physics, Emilio Segre Visual Archives.)

The Sharper Image for Surveillance



Livermore researchers imaged the University of California's Lick Observatory on Mount Hamilton with a remote-surveillance system from 60 kilometers away. (a) The unprocessed image is blurry. (b) The image produced using the speckle-processing technique is much clearer.

A technique adapted by Livermore scientists to take the twinkle out of stars is now being used to improve the resolution of long-range surveillance systems trained on earthbound objects. The speckle-imaging technique involves taking tens to hundreds of pictures with short-exposure times and reconstructing a single, sharp image using image-processing software.

The technique drew the interest of Livermore engineer Carmen Carrano. She developed a prototype remote-surveillance system that can produce a detailed image of a face from a couple of kilometers away. The system also helps identify vehicles tens of kilometers away and improves the viewing of large structures more than 60 kilometers away.

Short Exposures and Speckle Imaging

Typically, a person viewed 3 kilometers away with the naked eye appears as a small speck. Even high-power lenses yield little more than a blurry figure. The culprit is atmospheric turbulence, the same process that causes mirages to waver above hot asphalt on a warm day. In speckle imaging, several hundred pictures with short exposures are taken to freeze Earth's atmospheric turbulence. The enhanced surveillance system designed by Carrano incorporates the speckle-image-processing technique, which was first developed during the 1980s for astronomical applications. Speckle imaging has been used to obtain high-resolution astronomical images such as those of the Shoemaker–Levy comet hurtling into Jupiter, satellites orbiting Earth, and Saturn's moon Titan. (See *S&TR*, April 2000, pp. 17–18.)

To bring detail back into the blurry image of an object, astronomer's needed a way to subtract the effects of the intervening atmosphere. Speckle imaging does this by using many short-exposure frames of the same scene. Unlike a long-exposure image, which presents a low-resolution, uniformly blurry view of the object, short-exposure images effectively freeze the atmospheric aberrations, retaining high-frequency spatial information. A short-exposure image of a point target looks like a speckle pattern, hence the name of speckle imaging. These speckles are caused by the bending and refraction of light rays as they travel through the turbulent atmosphere.

Each short-exposure frame contains high-resolution information. However, because the image is distorted, many short-exposure frames are needed to reconstruct a sharper image. Averaging the short-exposure images together will result in merely another long-exposure image. Instead, amplitude and phase information characterizing the true image are separately calculated from Fourier transforms of the short-exposure images, using a complex set of averaging procedures that have been developed. These estimates of amplitude and phase are then processed by inverse-Fourier transform

to reconstruct a final, sharper image. A Fourier transform is a standard mathematical operation that converts data in one domain (for example, time) into data in another domain (for example, frequency). An inverse-Fourier transform converts the information back into the original domain. These mathematical transformations are often used to bring data into a domain that is easier to process computationally.

Processing the Image

"Astronomical imaging usually involves observing a bright, compact object, such as a star, in space," notes Carrano. "The atmospheric profile between the star and the telescope can be thought of as a shallow layer concentrated at or near the telescope pupil. But surveillance imaging is far more complex because the atmospheric turbulence is distributed over the entire path of observation, and the objects are extended over a larger field of view."

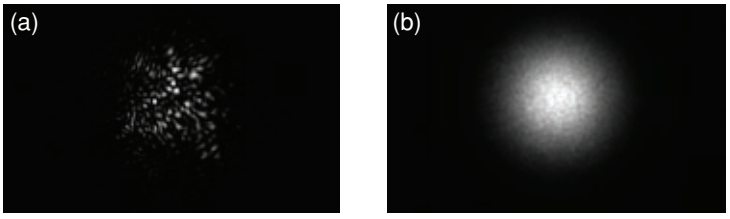
Carrano modified the original speckle-image-reconstruction software so it could process terrestrial imaging through distributed turbulence. The raw data are composed of a sequence of two-dimensional images, such as 100 1024- by 1024-pixel images. The first step is to account for any bad pixels or groups of pixels that were obscured by dust on the optics using a process called flat fielding, which divides each frame by a normalized reference frame of a flat field.

Next, a global frame-by-frame registration is performed. Carrano explains, "During the data collection, the telescope might be shaking slightly. That factor, along with certain atmospheric effects, leads to the frames shifting horizontally and vertically." Usually, the first frame is taken as the alignment reference, although the frame average can also be used as a reference. "We borrowed a trick from solar astronomy—breaking up the image sequence into small regions or tiles that overlap and then stitching them back together after processing," says Carrano. "This subfield processing, or tiling, can significantly improve the quality of the reconstructed image."

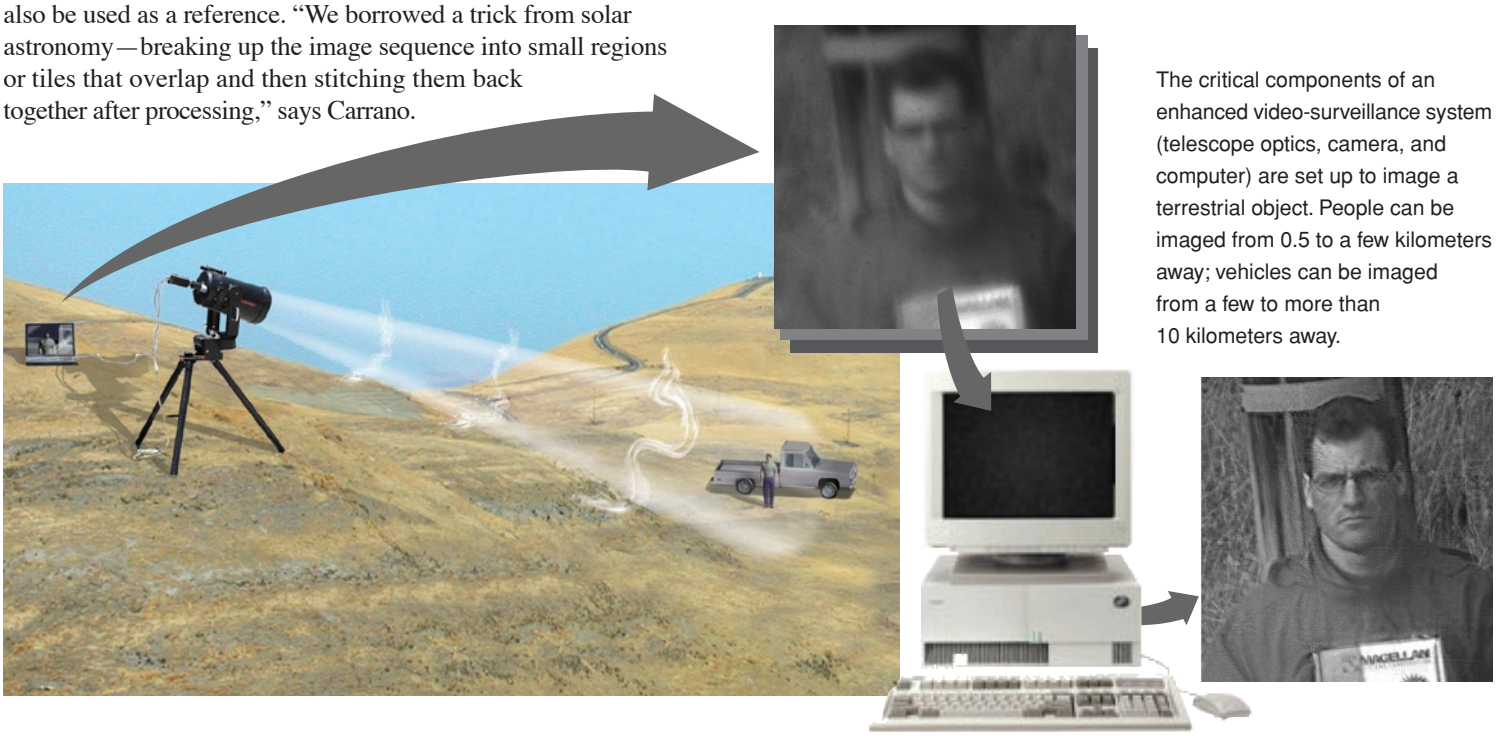
Processing to the diffraction limit for a sequence of 30 256- by 256-pixel images on a commercial laptop computer takes a few seconds, without any attempts to optimize the software. "By modifying the algorithm to continuously process data with a moving sliding window in time and implementing the algorithm into a digital-signal-processing hardware solution, we should be able to achieve the same results but in real time," says Carrano.

Bringing It into Focus

The team has conducted many experiments over the past few years to establish the performance of these enhanced surveillance techniques. The work was funded by the Engineering Directorate as a technology-base project. Such projects represent discipline-



(a) An image of a point source with a short-exposure time shows the speckle pattern caused by the atmosphere interfering with the light waves. (b) An image of a point source with a long-exposure time has a low resolution and is uniformly blurry.

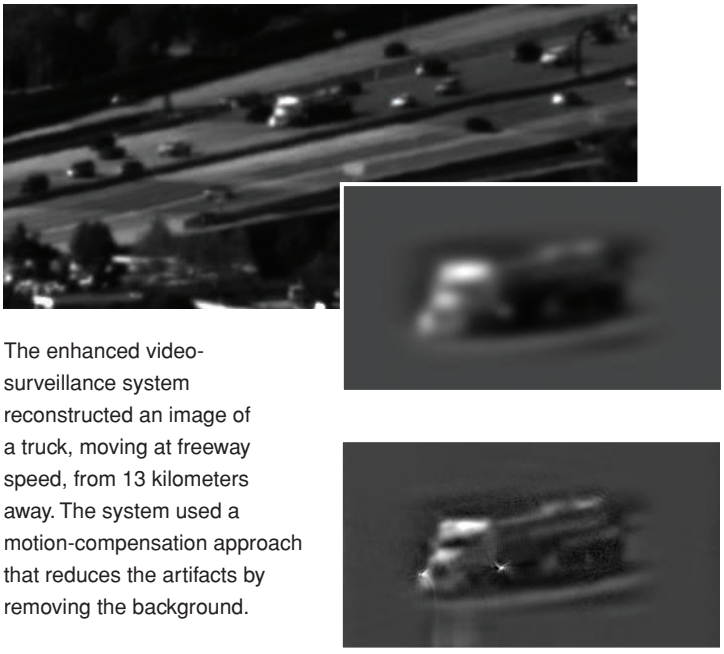


The critical components of an enhanced video-surveillance system (telescope optics, camera, and computer) are set up to image a terrestrial object. People can be imaged from 0.5 to a few kilometers away; vehicles can be imaged from a few to more than 10 kilometers away.

oriented, core-competency activities that are multiprogrammatic in application, nature, and scope. The National Nuclear Security Administration's Office of Nonproliferation Research and Engineering also funded the experiments and continues to fund the project. From creating a prototype remote-video-surveillance system and conducting initial experiments, Carrano has progressed to improving the image processing and conducting more experiments from a hillside location. She also demonstrated long-range face recognition—producing a facial image from nearly 1 kilometer away that was detailed enough to allow a correct match from a database of 685 people with commercial facial-recognition software.

"We also have been exploring ways to improve the system's real-time capability," says Carrano. "Earlier efforts required the object under surveillance to remain still during the 2 to 3 minutes required for data acquisition, after which it took from 10 to 30 minutes for the images to be processed with the prototype version of the software."

The real-time imaging system uses a video-rate charge-coupled-device (CCD) camera and a Cameralink-type frame grabber, whose user interface and data-acquisition capabilities were developed by Livermore engineer Dennis Silva. Carrano converted the image-processing software—originally prototyped in Fortran and IDL—into C-programming language. "These efforts increased the speed tremendously," notes Carrano. To further speed up the processing, she used a multiprocessor computer and parallelized the software over the server's four processors. For example, processing a sequence of 30 1024- by 1024-pixel images on four 1.9-gigahertz Xeon processors now takes 20 seconds instead of 60 seconds with a single processor on the same machine.



The enhanced video-surveillance system reconstructed an image of a truck, moving at freeway speed, from 13 kilometers away. The system used a motion-compensation approach that reduces the artifacts by removing the background.

The real-time camera system has been tested at a range from 1 to more than 20 kilometers away and is being used to image objects in motion, such as a vehicle moving through a stationary background. With appropriate preprocessing to track and isolate the moving object of interest within the image sequence, imagery of moving objects can be successfully enhanced. "Work remains to be done in this area," Carrano notes. "For instance, if the target is moving too fast, active-object tracking will be needed to capture enough frames for processing; we typically need at least 20 to 30 frames."

Carrano has also enhanced the system for use in low-light situations, such as during twilight and nighttime. By adding an image intensifier to the CCD camera, she was able to use only ambient light to obtain good quality images at twilight from 1.5 kilometers away. For nighttime viewing, she used an image intensifier on the CCD camera as well as a near-infrared illuminator on the targets to push the system into creating images in the near-infrared portion of the spectrum from a kilometer away. Finally, Carrano and her colleagues developed a simulation capability to predict performance for a variety of imaging scenarios.

The high-resolution imaging capability has drawn the interest of the Department of Defense and the intelligence community. As Carrano points out, it could be useful to any organization or company that needs a detailed picture of what is occurring at a distance, such as law enforcement personnel and wildlife researchers.

"We've made much progress in developing and demonstrating the speckle-imaging technique for long-range surveillance imaging since just over 4 years ago when it was only an idea," says Carrano. Eventually, in collaboration with industrial partners, we plan to create a compact, real-time system for use in the field."

—Ann Parker

Acknowledgments: Programmatic support: James Brase and Scot Olivier; experimental support: Doug Poland, Mike Newman, Jack Tucker, Kevin Baker, Kai LaFortune, and Scott Wilks; real-time-imaging software support: Dennis Silva; early consulting support: Don Gavel and Erik Johansson; radiometry and optics support: Brian Bauman; parallel simulation implementation: Jose Milovich.

Key Words: atmospheric turbulence, enhanced surveillance, speckle imaging, image processing.

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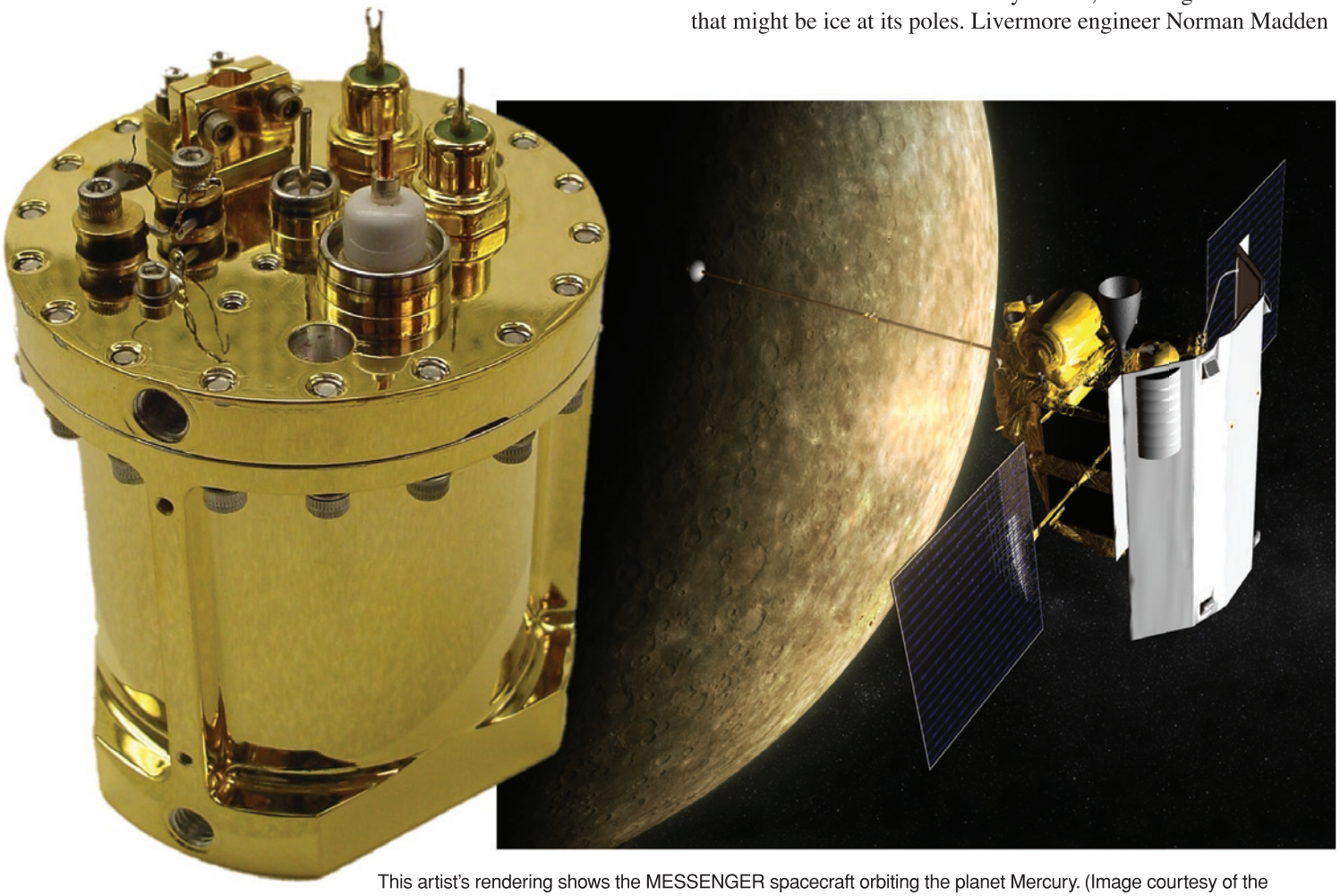
Keeping Cool Close to the Sun

THE germanium detector in the gamma-ray spectrometer (GRS) aboard the MESSENGER spacecraft is only the size and weight of a can of peaches but will play a critical role in investigating Mercury, the planet closest to the Sun. The MESSENGER (MErcury Surface, Space ENvironment, GEochemistry, and Ranging) spacecraft travels at about 38 kilometers per second and is named after the scientific goals of the mission. It is the first spacecraft to visit Mercury since 1975.

MESSENGER must take an oblique route to approach Mercury so that it does not fly past the planet and fall directly into the Sun. The spacecraft will travel 7.9 billion kilometers, flying by Earth once, Venus twice, and Mercury three times before settling into orbit around this mysterious planet. Of all the terrestrial planets, which include Venus, Earth, and Mars, Mercury is the smallest and the densest; its days are 176 Earth days long, two complete orbits of the planet around the Sun. Temperatures range from a high of 450°C on the Sun side during its long day to a low of –185°C on its night side. By studying this extreme planet, scientists hope to better understand how Earth formed and evolved.

The GRS, one of the seven lightweight scientific instruments on MESSENGER, will be used to help scientists determine the abundance of elements in Mercury's crust, including the materials that might be ice at its poles. Livermore engineer Norman Madden



This artist's rendering shows the MESSENGER spacecraft orbiting the planet Mercury. (Image courtesy of the National Aeronautics and Space Administration.) A gamma-ray spectrometer aboard the spacecraft will help scientists determine the abundance of elements in Mercury's crust. In the spectrometer, the germanium detector's crystal is hermetically encapsulated in a highly reflective gold-plated container to protect it.

led the West Coast team effort to design and build the GRS in a collaboration led by Johns Hopkins University Applied Physics Laboratory (JHUAPL). The team included Lawrence Berkeley and Lawrence Livermore national laboratories as well as University of California at Berkeley (UCB) Space Sciences Laboratory (SSL). The JHUAPL MESSENGER project is a National Aeronautics and Space Administration (NASA) Discovery Mission.

Detecting the Elements in Mercury's Surface

At the heart of the GRS is a germanium detector that will measure the gamma rays coming from Mercury's surface. Mercury is constantly bombarded with cosmic rays, and because it has almost no atmosphere, the planet's surface is activated and gives off gamma rays that are detectable from orbit. But not all gamma rays are alike. The energy of each gamma ray varies, depending on the type of element it comes from.

The germanium detector consists of a 5-centimeter-diameter, 5-centimeter-long germanium crystal that is electromechanically cooled and encapsulated in a highly reflective gold-plated container with a pressurized, ultrapure nitrogen-gas atmosphere. When illuminated by hard x rays or gamma rays, the germanium crystal releases electron hole pairs, which create a current as they are pulled to the inner and outer electrodes of the detector. This current pulse, which is proportional to the incident gamma-ray energy, is amplified and converted into digital data.

The data are accumulated and eventually compared to a catalog of element signatures. These signature gamma rays enable researchers to determine the elements that make up Mercury's surface. By counting the number of each type of gamma ray, researchers will also be able to determine the relative abundance of the elements.

Scientists have been puzzled by certain deposits in craters at Mercury's poles. Although most of Mercury experiences extreme heat during its long days, portions of these craters never get direct sunlight, and scientists wonder if the reflective material detected there could be ice. With the GRS data, scientists could determine whether these materials contain hydrogen in water ice or whether the deposits are formed of sulfur or some other element.

With its high energy resolution, the germanium detector obtains precise information from the planet's surface while it remains in space—but doing so is a challenge. The detector must be cooled to a very low temperature (about –185°C), and it must survive solar flares and repair itself when it accumulates radiation damage. Bombardment by energetic particles from the Sun and outer space (mostly high-energy protons) damages the germanium crystal and degrades the energy resolution. Damage is repaired by a process called annealing; the temperature of the crystal is slowly raised to 85°C and then sustained for a few days before being lowered back down to –185°C.

Keeping It Cool

Because the detector needs to operate at very low temperatures and MESSENGER is close to the Sun, the thermal design to protect the detector was critical. The detector is kept cool by an electromechanical cryocooler attached to the outside of the device. However, the cryocooler has a limited cooling capacity because of size and weight constraints.

To ensure the cryocooler would sufficiently cool the detector, Livermore scientists used SINDA/FLUINT, a commercial program originally developed by NASA, to model the thermal environments that the spectrometer was expected to encounter—during liftoff, in space while en route to Mercury, and in orbit around the planet. Using the data from the model, scientists from Lawrence Livermore and Lawrence Berkeley developed a design that included three closely spaced and highly reflective thermal shields held in place with DuPont KEVLAR® fiber.

Assembly Challenges

Assembling the detector, its heat shields, and its external cage was particularly challenging. All the pieces had to be held in place, with all the required gaps between them, while the KEVLAR® was strung in two directions around the cage under tension. Once assembled, the entire device had to be held in place while the epoxy glue holding the ends of the fiber cured over 24 hours.

When designing the assembly, the team found an article by Pat Roach at NASA Ames about using KEVLAR® to hold a cryogenic device in place and determined that particular fiber would also be appropriate for the GRS. The advantages of KEVLAR® are that it is very strong, has low heat conductivity, and does not outgas. However, during testing, the team did discover that the fiber frays. The team encountered problems when tying off the ends, and the fiber tended to fray when it was bent or in contact with a metal edge.

"We solved the fraying problem by widening the radius of the pegs and removing any sharp edges that were touched by the fiber," says Livermore engineer Monika Witte. "And instead of tying off the ends, we used an epoxy to glue the ends in place." This epoxy needed to meet NASA's specifications to ensure that no fumes from the epoxy could contaminate the detector or other scientific equipment on MESSENGER.

Once assembled, the device was tested to ensure that the acceleration and vibration during launching would not affect the fiber rigging, cryogenic cold finger, wire connections, or gaps between the detector, thermal shields, and external cage. Livermore performed sinusoidal and random vibration tests, during which the device was mounted on a shaker table and vibrated with constant amplitude through a range of frequencies. The test frequencies represented the full range of required test conditions without

All parts of the germanium detector assembly (right), its thermal shielding (center), and its external cage (left) are highly polished and gold-plated to minimize radiative-heat transfer.

exceeding limits and overstressing the instrument. The tests showed that the external cage was stiff enough to minimize disjointed vibration (where two parts of the GRS are vibrating at different rates) and flexible enough not to break under the strain.

The Best Kind of Collaboration

"This was truly a collaborative effort," says Madden. "All the team members had to work very closely and cooperatively together to make this project a success." The detector was designed and built by Lawrence Berkeley for JHUAPL. Lawrence Livermore performed the thermal analysis as well as the vibration analysis and testing. UCB's SSL fabricated the many space-qualified mechanical components. Lawrence Berkeley and Lawrence Livermore collaborated with SSL in assembling the detector, thermal shields, and cage device in a space-certified clean room.

Early Results

Launched on August 3, 2004, MESSENGER is on its six-and-a-half-year trip to Mercury. While traveling, the GRS is already recording gamma rays from space and with slightly better resolution than expected. In addition, the detector has undergone a scheduled anneal cycle. Scientists are excited about these promising early results and look forward to the data the GRS will obtain once in orbit around Mercury.

—Karen Rath

Key Words: gamma-ray spectrometer (GRS), germanium detector, KEVLAR® fiber, Mercury, MESSENGER, thermal shielding, vibration testing.

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Continued from p. 2

Better estimates of the solar nebula's lifetime

By studying some of the oldest objects in the universe, Laboratory physicist Ian Hutcheon and colleagues from the University of Hawaii at Manoa, the Tokyo Institute of Technology, and the Smithsonian Institution have found important clues about the lifetime of the solar nebula—the mass of dust and gas that eventually formed the solar system. In their project, funded by Livermore's Laboratory Directed Research and Development Program, the researchers measured the oxygen and magnesium content of chondrules and calcium aluminum–rich inclusions (CAIs), both components of the primitive meteorite Allende. Their results indicate that the oxygen in the solar nebula evolved rapidly over a span of 2 million years.

According to the team's measurements, CAIs are enriched with 4 percent more of the isotope oxygen-16 (^{16}O) than is found on Earth. (Different isotopes of an element vary in the number of neutrons in the nucleus of each atom.) This small amount of ^{16}O enrichment is a signature of the oldest objects in the solar system.

The team's results indicate that CAIs formed in an oxygen-rich environment about 4.567 billion years ago. Chondrules formed in an oxygen setting much like that on Earth and date to 4.565 billion years ago or less. Previous estimates of the solar nebula's lifetime ranged from less than 1 million years to 10 million years. Says Hutcheon, "Refining the lifetime of the solar nebula is significant in terms of understanding how our solar system formed." The team's results appeared in the April 21, 2005, issue of *Nature*.

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Each month in this space, we report on the patents issued to and/or the awards received by Laboratory employees. Our goal is to showcase the distinguished scientific and technical achievements of our employees as well as to indicate the scale and scope of the work done at the Laboratory.

Patents

Nondegenerate Optical Parametric Chirped-Pulse Amplifier

Igor Jovanovic, Christopher A. Ebbers
U.S. Patent 6,870,664 B2
March 22, 2005
This system provides input pump and single pulses. A first dichroic beam splitter is highly reflective for the input signal pulse and highly transmissive for the input pump pulse. A first optical-parametric amplifier nonlinear crystal transfers part of the energy from the input pump pulse to the input signal pulse resulting in a first amplified signal pulse and a first depleted pump pulse. A second dichroic beam splitter is highly reflective for the first amplified signal pulse and highly transmissive for the first depleted pump pulse. A second optical-parametric amplifier nonlinear crystal transfers part of the energy from the first depleted pump pulse to the first amplified signal pulse resulting in a second amplified signal pulse and a second depleted pump pulse. A third dichroic beam splitter receives the second amplified signal pulse and the second depleted pump pulse. The second depleted pump pulse is discarded.

Porous Protective Solid-Phase Micro-Extractor Sheath

Brian D. Andresen, Erik Randich
U.S. Patent 6,871,556 B2
March 29, 2005
A porous protective sheath for active extraction media used in solid-phase microextraction permits exposure of the media to the environment without the necessity of extending a fragile coated fiber from a protective tube or needle. Subsequently, the sheath can pierce and seal using gas chromatography and mass spectrometry septums, allowing direct injection of samples into inlet ports of analytical equipment. Using a porous protective sheath, within which the active extraction media is contained, mitigates the problems of (1) fiber breakage while the fiber is extended during sampling, (2) active media-coating loss caused by physical contact of the bare fiber with the sampling environment, and (3) coating slough-off during fiber extension and retraction operations caused by rubbing action between the fiber and protective needle or tube.

Shape-Memory Alloy and Shape-Memory Polymer Tools

Kirk P. Seward, Peter A. Krulevitch
U.S. Patent 6,872,433 B2
March 29, 2005
Composite shape-memory alloy (SMA), shape-memory polymer (SMP), and combinations of SMA and SMP are used to produce microelectromechanical tools, such as catheter distal tips and actuators, for minimally invasive techniques including microsurgery. Applications for these tools include a method for reversible fine-positioning of a catheter tip; a method for reversible fine-positioning of tools or therapeutic catheters by a guide catheter; a method for bending articulation through the body's vasculature; methods for controlled stent delivery, deployment, and repositioning; and catheters with variable modulus, vibration mode, inchworm capability, or articulated tips. These actuators and catheter tips are bistable and opportune for in vivo usage because the materials are biocompatible and convenient for intravascular use and other minimally invasive techniques.

Semiconductor Material and Method for Enhancing Solubility of a Dopant Therein

Babak Sadigh, Thomas J. Lenosky, Tomás Díaz de la Rubia, Martin Giles, Maria-Jose Caturla, Vidvuds Ozolins, Mark Asta, Silva Theiss, Majeed Foad, Andrew Quong
U.S. Patent 6,872,455 B2
March 29, 2005
A method for enhancing the equilibrium solubility of boron and indium in silicon involves first-principles quantum-mechanical calculations to determine the temperature dependence of the equilibrium solubility of two important p-type dopants in silicon, namely boron and indium, under various strain conditions. The equilibrium thermodynamic solubility of size-mismatched impurities, such as boron and indium in silicon, can be raised significantly if the silicon substrate is strained appropriately. For example, for boron, a 1-percent compressive strain raises the equilibrium solution by 100 percent at 1100°C. For indium, a 1-percent tensile strain at 1,100°C enhances the solubility by 200 percent.

Hybrid Chirped-Pulse Amplification

Christopher P. J. Barty, Igor Jovanovic
U.S. Patent 6,873,454 B2
March 29, 2005
This hybrid chirped-pulse amplification system features a short-pulse oscillator. The oscillator pulse is stretched to produce an oscillator seed pulse. A pump laser generates a pump-laser pulse. The stretched oscillator-seed pulse and the pump-laser pulse are directed into an optical-parametric amplifier, producing an output-amplified signal pulse and an output-unconverted pump pulse. The output-amplified signal pulse and the output laser pulse of the optical-parametric amplifier are directed into a laser amplifier producing a laser amplifier output pulse. The laser amplifier output pulse is compressed to produce a recompressed hybrid chirped pulse.

Liposuction Cannula Device and Method

Paul J. Weber, Steven R. Visuri, Matthew J. Everett, Luiz B. Da Silva, Alwin H. Kolster

U.S. Patent 6,875,207 B2

April 5, 2005

This liposuction apparatus has an optional sonic or ultrasonic source. The sonic or ultrasonic source has an axial lumen passage in which the shaft can be made to reciprocate (oscillate) nonrectilinearly. The apparatus may also use rectilinear reciprocation motion and ultrasonic motion or energy along its shaft. The liposuction apparatus has many advantages such as a nonrectilinear single-shaft reciprocating cannula, a sonic or ultrasonic energy that is delivered to the distal tip, and a rectilinear reciprocating cannula with ultrasonic energy along the shaft from the handle. All of these reciprocating components are powered by excess vacuum capacity in the liposuction's aspirator (suction engine). Three primary sources of energy are applied to the cannula shaft: the oscillating surgeon's arm motion of approximately 1 to 2 hertz; the reciprocating motion of about 100 hertz; and the optional concomitant motion delivered by the ultrasonic energy of, for example, 25 kilohertz.

Light Metal Explosives and Propellants

Lowell L. Wood, Muriel Y. Ishikawa, John H. Nuckolls, Philip F. Pagoria, James A. Viecelli

U.S. Patent 6,875,294 B2

April 5, 2005

These light metal explosives, pyrotechnics, and propellants (LME&Ps) are composed of a light metal component such as lithium, boron, beryllium, or their hydrides. They may also be composed of intermetallic compounds and alloys containing these elements as well as an oxidizer component containing a classic explosive, such as CL-20, or a nonexplosive oxidizer, such as lithium perchlorate, or combinations thereof. LME&P formulations may have light metal particles and oxidizer particles ranging in size from 0.01 to 1,000 micrometers.

Awards

Dona Crawford, associate director of Computation, was named the **2005 Outstanding Woman of the Year** in the science category by the **Alameda County Women's Hall of Fame**. She was honored for her work and leadership in establishing the world's fastest supercomputer, called BlueGene/L, at Livermore. Crawford joined the Laboratory in 2001. Prior to that, she spent 25 years in computer science at Sandia National Laboratories in Livermore and New Mexico. The Alameda County Women's Hall of Fame was established in October 1993 to recognize outstanding women in the California county for their achievements and contributions to the county and its citizens.

In May, **James Berryman** of the Energy and Environment Directorate was awarded the **2005 Maurice A. Biot Medal** by the **American Society of Civil Engineers** at the 3rd Biot Poromechanics Conference in Norman, Oklahoma. He received the award for "his outstanding contributions in poromechanics, granular materials, random composite media, tomography and inverse problems, and seismology." Since 1981, Berryman has been a physicist at the Laboratory, and he is currently a member of the Computational Physics Group in the Earth Sciences Division. He has been a consulting professor of geophysics at Stanford University since 1992. The Biot Medal is named after Maurice A. Biot, who during a career spanning more than 50 years, made an unusually broad range of contributions in science and technology.

Abstracts

Mining Genomes

Although reliable methods for identifying genes exist, a significant challenge remains in identifying regulatory elements, which are the sequences of DNA that interact with specific proteins to serve as on and off switches for genes. Of particular interest to many biologists are so-called gene deserts, the large and seemingly barren areas located between genes. Department of Energy researchers have shown that gene deserts contain large numbers of regulatory elements. In an effort to help researchers locate them in published genome sequences of many different species, Ivan Ovcharenko and colleagues from Lawrence Livermore and Lawrence Berkeley national laboratories and Pennsylvania State University have developed a suite of analytical and visualization computational tools. The interactive tools are Web accessible and can be easily used by researchers who have minimal or no computer training. Every day, more than 300 researchers worldwide use the Livermore tools, which compare DNA from different species.

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Shedding Light on Quantum Physics

Livermore physicists using x-ray lasers and single-photon counting experiments to probe the mysteries of materials behavior and biological processes base much of their work on the tenets underlying two papers published by Albert Einstein early in the last century. The first paper, published in 1905 in the German journal *Annalen der Physik*, was one of a series of papers Einstein published that year ushering in the era of modern physics. In that paper, using the previously observed photoelectric effect as the proof, Einstein put forth a theoretical explanation of light as a stream of particles.

The second Einstein paper that set the stage for future discovery of the laser was published in 1917 and entitled "On the Quantum Theory of Radiation." In this paper, Einstein continued his inquiry into the properties of light and matter with an explanation of how radiation is absorbed and emitted by atoms. Livermore's pioneering laser research is based on these phenomena.

World Year of Physics events at Livermore:
www.llnl.gov/pao/WYOP.

U.S. Government Printing Office: 2005/783-059-10008

Mission Control for Laser Experiments

The computer control system for the National Ignition Facility directs more than 60,000 devices.

Also in July/August

- *Einstein's work on Brownian motion made the atomic realm visible and is the basis for many Livermore projects.*
- *Nonbiological production of methane in Earth's mantle could potentially provide unlimited energy.*
- *Experimental results from a Livermore project contradict claims of the accelerated release of energy from the nuclear isomer hafnium-178.*

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